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SURGICAL POSTURE: WITH SYMBOLS FOR ITS RECORD ON THE ANESTHETIST'S CHART

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THE result of a surgical operation often depends upon details which may seem unrelated but which really are essential to success. Attention to physical abnormalities found at preliminary examination, preparation of the patient, preanesthetic medication, proper anesthetic dosage, operating room temperature, drafts of air in operating room, corridor or patient's room, even such a simple thing as a tight neckband on the patient's operating gown, may tip the scale, delicately poised, between recovery and death. Of these details so closely linked with success, surgical posture is especially noteworthy. A patient died after a breast operation because she was lifted from the dorsal to the sitting position for application of the bandage. Deaths have resulted from ill-advised use of the Fowler post-operative posture. The prone posture has a bad reputation, justified by experience.

Before the advent of anesthesia, all other factors of operative posture were subservient to the necessity for firmly securing the patient to an immovable foundation. Heavy chairs and tables to which the patient could be securely bound answered all requirements. The first instance of a surgical posture designed to facilitate a particular operation was the lithotomy position, employed for the operation of perineal lithotomy. Between 1860 and 1870, Freidrich Trendelenburg popularized the high pelvic posture, also designed for the operation of lithotomy, but by the supra-pubic route. The high pelvic posture had already been described by Bardenhauer of Cologne but was extensively used and recommended by Trendelenburg. It was correctly described by Esmarch in his "Surgical Technic" of 1873 under the head, "Suprapubic Cystotomy." "For this operation, Trendelenburg's position is generally employed. By raising the trunk and legs of the patient, his body is placed in an oblique position of 45 degrees." In this country the high pelvic position was described in the first (1892) edition of Keen and White's Surgery with due credit to Bardenhauer as the first to appreciate the advantages of the position. In subsequent editions the name, Bardenhauer, was forgotten.

The name Trendelenburg exercises a strange fascination on the

minds of surgeons and surgical writers. While the Trendelenburg position is a distinct entity, elevation of the pelvis to an angle of 45 degrees and maintenance of this inclination by flexing the knees, we read of "High Trendelenburg," "Low Trendelenburg," and "Reverse Trendelenburg." "Trendelenburg Anesthesia" proves to be the administration of the anesthetic agent with the patient in the head lowered oblique position. Patients are "Trendelenburged" and "Reverse Trendelenburged."

Trendelenburg early found that his high pelvic position was not free from danger and advised against its use for fat patients. Kraske found that the Trendelenburg position was likely to cause an acute dilatation of the heart in patients who suffered from myocardial disease. Experience has proved the validity of these objections to the routine use of the Trendelenburg position and has shown that some other of the surgical postures are equally dangerous. A posture which would be trying to a conscious subject is not only equally injurious to an anesthetized patient but its harmful effect is intensified by the tissue relaxation which is a part of the action of the anesthetic agent. The fat dowager who must have her head supported on several pillows in order to sleep comfortably will be as seriously handicapped by the Trendelenburg position while anesthetized as if she were conscious. A posture recommended for perineal prostatectomy is identical with a position devised in medieval times as a form of torture. Its effect on a patient with aged hardened arteries has often been fatal. The Fowler post-operative posture, with the force of gravitation draining into the lower extremities the blood supply essential to the cerebral centers, already depleted by shock or hemorrhage, has been responsible for many fatalities.

In each of the surgical postures, the effect of the pull of gravity on the circulatory and respiratory systems must be considered, especially when the efficiency of the circulation and respiration is impaired by abnormality, by disease, or from the effect of the anesthetic agent. Postures with the head lowered are more favorable to the circulation; with the head raised, more favorable to the respiration. The dorsal posture with the head slightly lowered is most favorable to anesthetized patients and should be chosen for those whose condition is doubtful or critical.

The prime function of the combined respiratory and circulatory systems is to supply oxygen to the tissues. While the other tissues can survive without oxygen for a longer period, a lack of oxygen to the cerebral centers is likely to prove fatal within a very few minutes. Fortunately we are able to control to a considerable extent the cerebral blood pressure and the resulting cerebral blood supply by changes in posture. With the subject in the horizontal position, the systolic and diastolic pressures are usually the same when taken at the elbow or at the knee. In the erect posture, the pressure taken at the knee is higher than the brachial pressure by an amount equal to the weight of a column

of blood reaching from the knee to the elbow. The pressure taken at the level of the brain is correspondingly lower than that taken at the cardiac level. Keeping in mind the fact that one inch of water balances two mm. of mercury, we would expect to find that, in the erect posture, the systolic and diastolic pressures would be raised about 50 mm. of mercury at the level of the knee and diminished about 20 mm. at the level of the brain, when compared with pressures taken at the cardiac level. These theoretical results check closely with the practical findings. In the erect posture, systolic and diastolic pressures are uniformly higher at the knee than at the cardiac level; systolic and diastolic pressures are lower at the level of the brain than at the cardiac level; the pulse pressure is the same at each of the three levels. In comparison with brachial pressures, the cerebral systolic and diastolic pressures are increased when the head is lowered and diminished when the head is raised.

From the work of Ellis at the Medical Research Laboratory of the Air Service, at Mitchell Field, Long Island, and others, we learn the immediate effect of passive postural tilts on healthy subjects. Tilts raising the head result in an increase in the pulse rate, a fall in systolic pressure, and a rise in diastolic pressure, with corresponding diminution in pulse pressure. Tilts in which the head is lowered result in a fall in pulse rate, an increase in systolic pressure, and a fall in diastolic pressure, with a corresponding increase in pulse pressure. When the head is raised, the result is the same when the inclination is 45 degrees from the horizontal as when the tilt reaches the vertical position. The increase in diastolic pressure which accompanies a change from the horizontal to the erect posture indicates the vaso-motor response to the change. Contraction of the splanchnic arterioles prevents massive accumulation of blood in the abdominal viscera with resulting cerebral anemia. Under a light degree of anesthesia the vaso-motor mechanism is not interfered with, but in the deep anesthetic zones accompanied by perfect muscular relaxation, the vaso-motor compensation for postural changes is interfered with seriously. If then the head is raised, or even placed in a horizontal posture, so large a proportion of the entire mass of blood may collect in the abdominal veins that the supply to the heart may be insufficient and a severe cerebral anemia may develop. In this condition knowledge of the gravitational effects of posture may be of essential importance. With the dorsal postures in which the head is raised, the blood pressure must be carefully watched. A steadily declining systolic and diastolic pressure with an increasing pulse rate indicates that the head must be lowered before a serious cerebral anemia develops.

The theory of the peripheral causation of surgical shock provides the best working basis for the anesthetist. According to this theory the abdominal muscles relax, blood stagnates in the abdominal veins, with resulting failure in the supply of fluid to the right side of the heart, with failure in the blood supply to the cerebral centers and

resulting anoxia of brain cells. When imminence of shock is indicated by falling blood pressure, we must put the patient in the dorsal position with the head slightly lowered. This measure, combined with an excess of oxygen in the inspired air and intravenous glucose in saline, has so far seemed to be the most efficient treatment for impending surgical shock.

In the prone posture the patient is likely to show a dangerous fall in blood pressure, especially if he is moved from the dorsal to the prone posture while under the influence of the anesthetic. The change from the dorsal to the sitting position is almost equally dangerous. There have been numerous instances when a patient anesthetized in the dorsal position has become pale and pulseless when moved to the sitting posture preliminary to a tonsil operation. When the sitting posture is required for an adult, he should be anesthetized in this position. Children, anesthetized in the dorsal position, must be closely watched when they are lifted into the sitting position for the performance of an operation and must be promptly replaced in the horizontal posture if they show signs of cerebral anemia.

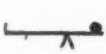
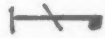
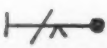
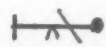
Intercostal paralysis, a constant associate of the third plane of surgical anesthesia, has a peculiar effect on patients in the prone posture. When an anesthetized patient is placed lying with the face downwards on the firm flat surface of an operating table the diaphragmatic movements are immediately impeded by the weight of the body resting upon the abdomen. The thoracic muscles being paralyzed, the diaphragm attempts to carry on the task of respiratory movement with an effort shown by perceptible lifting of the buttocks with each inspiration. Soon this movement ceases as the paralyzed thoracic muscles with difficulty take up the respiratory load with movements of lessened amplitude but increased frequency; a picture of labored, insufficient respiratory action which may aid in explanation of the state of prostration which has often accompanied protracted employment of the prone posture. Efforts to improve the thoracic movements by raising one shoulder on a pillow have not been very successful. Instead the diaphragmatic respiration must be restored. This can be done by placing a small pillow transversally underneath the anterior superior iliac spines. Diaphragmatic movements then proceed normally. Whenever the thoracic respiration has been paralyzed by the action of an anesthetic, efforts should be concentrated on freedom of diaphragmatic movement.

Before the induction of anesthesia the patient should be so placed as to require little moving about to secure the posture required for the operation. He should be made as comfortable as possible. Certainly he should have as many pillows under his head as he is accustomed to. Because he is to undergo an operation is no reason for depriving him of pillows or for making him unnecessarily uncomfortable. After the anesthesia has been administered pillows may be removed if there is any sensible reason for so doing. For the comfort of the patient the

reflex abdominal posture has distinct advantages. In the dorsal, supine position, the patient lies on a flat, level surface. The abdominal muscles as well as the hamstrings are on the stretch and the back is unsupported. The reflex abdominal is a modification of the dorsal posture in which the head is raised on one or more pillows, the shoulders are slightly elevated on a thin pillow, the hips and knees are slightly flexed by a pillow under the popliteal space and the hollow of the back is supported by a pillow of proper size. This posture favors relaxation of the abdominal muscles and should be chosen for most operations.

If the patient has been moved on the table after he has lost consciousness, the neck-band of the operating room gown should be inspected to see that it has not been pulled tight over the trachea and larynx. Skilled anesthetists have encountered serious difficulty from respiratory obstruction due to neglect of this simple precaution.

Surgical posture is of sufficient importance to warrant its record on the anesthetist's chart. For this purpose we use a system of symbols which are self explanatory and capable of modification to suit individual ideas. A number of the symbols are here shown:

Posture	Symbol	Posture	Symbol
Dorsal		Prone	
Right lateral		Left lateral	
Head raised Fowler		Head lowered Sculletus	
High pelvic Trendelenburg		Lithotomy	
Vertical		Dorsal recumbent	
Elliott		Dorsal elevated	
Robson		Jack-knife	
Thyroid		Edebohls	
Gall bladder		Left semi-prone	
Right kidney		Left kidney	

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STUDIES OF VINETHENE AS AN ANESTHETIC AGENT[1]

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Introduction

Studies of the effect of vinethene on cardiac automaticity as measured by the response to the injection of various sympathomimetic drugs were begun in an attempt to compare this agent to cyclopropane, chloroform, and diethyl ether, as previously reported (1), (2). The plan was to determine the effects produced by adrenalin, cobefrin, and neosynephrin on the same animals, as had been done with the other anesthetic agents. Early difficulties encountered led to further studies. This report deals not only with cardiac effects during vinethene anesthesia, but also with its effects on blood pressure, gastro-intestinal activity, nervous stimulation, kidney function, and liver damage in the dog.

Procedure and Results

Vinethene, which consists of divinyl ether 96.5 per cent. and ethyl alcohol 3.5 per cent. with 0.01 per cent. phenyl-alpha-naphthylamine as a preservative, was used in all the studies here reported.

Each vinethene induction was made by the open drop technique. Then an endotracheal tube with an inflatable cuff was inserted. Unless otherwise indicated anesthesia in the dog was maintained by the closed system as previously employed (1), the animal being connected to the anesthetic reservoir by way of a soda-lime carbon dioxide absorber.

The anesthetic mixture was supplied from a large Tissot spirometer. Freshly opened vinethene which had not passed date of expiration was always used. Vaporization was brought about by passing pure oxygen through 60 to 75 cc. of vinethene, to make a total volume of 75 liters. The volume was kept constant by replacing oxygen as it was used metabolically. The animals were maintained in surgical anesthesia so that there was only partial intercostal paralysis. The concentration of vinethene in the spirometer required for such anesthesia was determined routinely with the iodine-pentoxide train and found to be 10 to 12 per cent. If the animals were premedicated, a concentration of 8 to 9 per cent. vinethene was found to be adequate. Each anesthetization was carried out by an experienced member of the department of anesthesiology.

[1] Aided in part by grants from the Wisconsin Alumni Research Foundation, and Merck & Co., Inc.

Cardiac Automaticity and Conduction

Electrocardiograms taken before anesthetization and again after 40 minutes' surgical anesthesia were compared for the first 10 animals for rate, rhythm, P-R interval, and height of QRS complex and T wave. As indicated in Table 1, surgical anesthesia with vinethene caused S-A

TABLE 1

ELECTROCARDIOGRAPHIC FINDINGS IN LEAD II IN THE DOG BEFORE (CONTROL) AND DURING DEEP SURGICAL VINETHENE, AFTER 40 MINUTES' EQUILIBRATION AGAINST A CONSTANT MIXTURE

Dog	S-A Rate		P-R Interval (Seconds)		QRS (Millivolts)		*T Wave (Millivolts)	
	Control	Vinethene	Control	Vinethene	Control	Vinethene	Control	Vinethene
1	130	175	0.11	0.09	3.2	3.2	+0.2	−0.6
2	107	200	.08	.09	3.4	3.0	−0.6, 0.4	−1.0
3	110	167	.11	.09	3.2	3.2	0.6	+0.8
4	110	150	.10	.08	3.2	2.6	1.0	−0.6, 0.4
5	185	225	.10	.10	2.0	1.4	0.2	0, 0
6	130	150	.10	.08	3.4	3.2	−0.2, 0.2	−0.3
7	136	180	.10	.09	2.6	2.6	1.2	0.4
8	115	180	.10	.08	1.6	1.8	0.2	−0.4
9	110	167	.12	.11	3.5	1.2	1.2	−0.1, 1.0
10	118	200	.11	.08	2.4	1.0	−0.1, 0.1	0.2
Averages	130	179	0.103	0.089	2.85	2.32		

* Both negative and positive readings are indicative of a diphasic wave.

acceleration in every animal. In 8 of the 10 the P-R interval decreased by 0.01 to 0.03 second; in one instance there was no change, and in the other there was an increase of 0.01 second. The shortened P-R interval was undoubtedly due to the faster heart rate. The QRS complexes decreased in 6 of the 10 experiments by 0.2 to 2.3 millivolts. The T wave became more positive by 0.1 to 0.8 millivolt in 8 of the 10 anesthetizations and more negative by 0.2 millivolt in the other 2. Irregularities were not noted even in anesthesia that was prolonged for 2 to 3 hours.

The stimulating or sensitizing effect of vinethene on the automatic tissue of the dog's heart as measured by the occurrence of arrhythmias following a standard injection of adrenalin was determined as reported for other agents (1). Lead II electrocardiograms were taken throughout, and 40 minutes' minimal time was allowed for equilibration against the constant anesthetic mixture. Responses to the injection of equivalent pressor doses of neosynephrin and cobefrin also were observed. Toxic effects of marked weight loss, depression, and bloody diarrhea resulted in the death of 12 animals from a group of 17, and only 4 could be tested with all 3 sympathomimetic amines.

From Table 2 it will be seen that the control injection of 0.01 mgm. per kilogram of adrenalin in 5 cc. saline at the rate of 1 cc. per 10

seconds, which had been found previously as the desirable dose and rate of injection in studies of cardiac automaticity, caused A-V block in 9 experiments; A-V extrasystoles in 7; A-V rhythm in 9; ventricular extrasystoles in 7; slow ventricular rhythm in 2; and ventricular tachycardia in 2 experiments. Injection of the same dose of the amine into 12 animals under vinethene produced A-V extrasystoles in 2 instances and A-V rhythm in 4. When 11 of the dogs were premedicated with 1 mgm. morphine sulphate and 0.04 mgm. scopolamine per kilogram subcutaneously 45 minutes before induction, A-V block occurred once; A-V rhythm 5 times; ventricular extrasystoles and tachycardia once each and S-A acceleration 4 times.

TABLE 2

CARDIAC ARRHYTHMIAS RESULTING FROM INJECTION OF BLOOD PRESSURE RAISING DRUGS IN DOSES EQUIVALENT IN EFFECTIVENESS TO THE STANDARD ADRENALIN DOSAGE DURING DEEP SURGICAL VINETHENE ANESTHESIA AND IN VINETHENE ANESTHESIA FOLLOWING PREMEDICATION WITH MORPHINE 1.0 MGM./KG. AND SCOPOLAMINE 0.04 MGM./KG.

Procedure		Number of Animals	Equivalent Pressor Dosage to 0.01 Adrenalin	A-V block	A-V Extrasystoles	A-V Rhythm	Ventricular Extrasystoles	Slow Ventrical Rhythm	Ventricular Tachycardia	S-A Tachycardia
			mgm./Kg.							
Adrenalin	Control	13	0.01	9	7	9	7	2	2	0
	With vinethene	12	0.01	0	2	4	0	0	0	0
	Premedication with vinethene	11	0.01	1	0	5	1	0	1	4
Neosynephrin	Control	6	0.05	5	1	0	1	0	1	0
	With vinethene	5	0.05	0	2	2	1	0	0	0
Cobefrin	Control	5	0.025 to .0375	4	5	3	1	2	1	0
	With vinethene	5	0.025 to .0375	0	0	2	0	0	0	2

Control injection of the comparable pressor dosage of neosynephrin (0.05 mgm. per kilogram) in 6 animals produced A-V block 5 times; and A-V extrasystoles, ventricular extrasystoles, and ventricular tachycardia once each. In 5 of the animals anesthetized with vinethene, injection of neosynephrin was followed by 2 instances each of A-V extrasystoles and A-V rhythm and one of ventricular extrasystoles. Control injection of cobefrin (0.025 to 0.0375 mgm. per kilogram) into 5 animals gave results comparable to those with adrenalin. A-V block occurred 4 times; A-V extrasystoles 5; A-V rhythm 3; slow ventricular rhythm 2; and ventricular extrasystoles and tachycardia once each. Injection under vinethene elicited A-V rhythm and S-A tachycardia twice each.

It is evident that vinethene gave no evidence of having sensitized the heart to these drugs.

Blood Pressure and Blood Oxygen

Blood oxygen determinations were made by the van Slyke-Neill manometric method as modified by Shaw and Downing for diethyl ether (3). Duplicate analyses were done routinely. The first sample under vinethene was never drawn until at least 40 minutes of equilibration against the constant mixture. Depth of anesthesia was then varied by open drop administration and blood pressure recorded by the usual method of arterial cannulation. Blood samples were drawn at various planes of anesthesia. Figure 1 indicates blood pressure decreased with

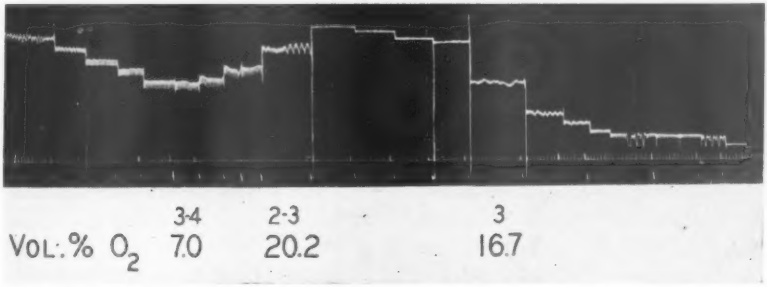

FIG. 1. Blood pressure variation with alteration in depth of vinethene anesthesia. Upper numerals are the planes of surgical anesthesia as given in Table 3. Vol. per cent. O_2 are averages of duplicate analyses of blood oxygen content.

TABLE 3

VOLUMES PER CENT. OF OXYGEN IN ARTERIAL BLOOD FROM DOGS BEFORE AND DURING VINETHENE ANESTHESIA MAINTAINED BY OPEN DROP TECHNIQUE. ALL FIGURES ARE AVERAGES OF DUPLICATE ANALYSES.

Dog No.	Arterial Blood Oxygen Content		Plane of Surgical Anesthesia*	Remarks
	Control	Vinethene		
	Volumes Per cent.	Volumes Per cent.		
T	14.6	21.4	2	
U	21.0	16.8	3	
V	20.7	19.6	3	
W	18.5	16.7	3	
X	15.2	9.8	3—4	Anesthesia deepened until running movements abolished
Y	21.8	7.0	3—4	Anesthesia deepened until running movements abolished, then lightened, and again deepened slightly
		20.2	2—3	
		16.7	3	

* Varying from no intercostal involvement (plane 2) to complete intercostal paralysis (plane 4).

increased depth of anesthesia. Table 3 shows that adequate oxygenation was maintained under vinethene except when the depth of anesthesia was carried to complete intercostal paralysis which was done with dogs X and Y to study running movements and blood pressure effects.

Running Movements

In each of 108 surgical vinethene anesthetizations to 46 dogs, there was some degree of aberrant muscular movement, which ranged from twitches to coordinated activity of all 4 extremities, simulating running movements. Not until there was complete intercostal paralysis could these be eliminated in all animals. The activity usually disappeared in the fore limbs before the hind limbs. This type of coordinated muscular response has never occurred in over 400 anesthetizations with chloroform, cyclopropane or diethyl ether. In 4 of 13 animals premedicated with morphine-scopolamine such responses also were noted under vinethene.

In an attempt to determine the site of stimulation for such muscular activity 4 dogs were anesthetized with vinethene and then decerebrated by the "bloodless" method of Sollmann (4). Transection of the brain stem at the level of the corpora quadrigemina was verified by examination after formalin fixation. The aberrant movements continued in 3 of the 4 cases. Further localization was evident when 1 of 3 animals in which the spinal cord had been transected at T-10 had continuation of the movements in the hind limbs. In this latter group there was a 5-day interval between cord transection and vinethene administration. Evidently the stimulation which gives these movements is in the cord itself.

Gastro-intestinal Activity

Two dogs were prepared with Thiry and Thiry-Vella loops of the jejunum for recording activity by the balloon-mercury-manometer and bolus propulsion methods. Gastric activity was determined simultaneously by means of a balloon-water-manometer-tambour system.

The unpremedicated dogs were trained to lie on the table unrestrained while breathing through a mask which could be coupled to the spirometer containing the vinethene-oxygen mixture. In this manner records could be obtained with a minimum of excitement during induction. They were then maintained at any desired plane of surgical anesthesia. The animals were anesthetized not more than once in two weeks for periods varying from 25 to 75 minutes.

Gastric tonus increased slightly with surgical anesthesia. Occasionally after discontinuing the agent there was an abrupt fall of tonus, which soon returned to the preanesthetic level. Gastric contractions were inhibited completely by anesthesia. Recovery began in 1 to 5 minutes after discontinuing the vinethene but usually it was not com-

plete in less than one hour. An esophageal cuff around the tube to the stomach balloon facilitated the aspiration of the profuse salivary secretion produced by vinethene. With this procedure the usual retching and vomiting during recovery was prevented, thus permitting studies in this period.

There was complete inhibition of propulsive and non-propulsive movements of the intestine and a marked loss of tonus in all planes of vinethene anesthesia. Thiry-Vella loops that normally closely accommodated sponge rubber boluses which measured 1 × 2 cm. would readily permit the introduction of the middle finger. When a bolus was introduced immediately before induction, it did not reappear until several minutes after the anesthetic was discontinued. For more than half an hour after anesthetization propulsion times were 1 to 5 minutes longer than the controls. Recovery of non-propulsive movements began within 4 minutes and was complete within 10 minutes after cessation of the administration of vinethene. When the animals were premedicated with morphine-scopolamine, non-propulsive activity of the intestine continued until the third plane of surgical anesthesia was reached.

Kidney Function

Oliguria or anuria occurred in 13 administrations to 5 dogs in which normal urine flows had been determined before anesthetization, as had

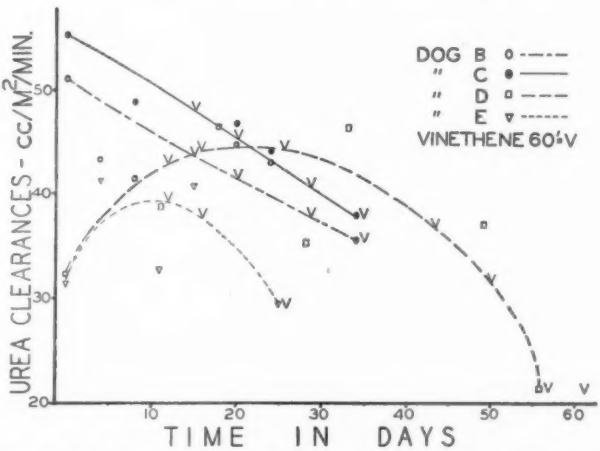

FIG. 2. Effect of vinethene on kidney function as determined by maximal urea clearances. Anesthesia was given for one hour each week, oxygen being used as the diluent for the agent. Each value is the average of clearances for three 20-to-30-minute periods. Dogs B and C died of acute yellow atrophy.

been observed previously with the other agents studied. The effects of vinethene on kidney function, as measured by urea clearance tests, were

determined on 4 dogs, employing the technique for maximal clearances as previously used (5). The control clearances of at least 3 sets of 3 periods each averaged 42.6 cc./M.²/minute. The average of the final set obtainable from the animals was 32.0 cc./M.²/minute. Anurias of several days' duration following the sixth and seventh administrations prevented further determinations in dog D. It may be noted from Fig. 2 that the smoothed curve for each animal declines progressively. Using the clearance method vinethene is thus shown to interfere with kidney function.

Dog F was followed before and after each of 7 hourly chloroform anesthetizations given at intervals of a week. The control urea clearances averaged 58.3 and those following anesthetization 57.2 cc./M.²/minute.

Liver Pathology

Eighteen rats in two different groups were used to study the effects of vinethene on the liver. Animals of each group were killed without any anesthesia in order to obtain control liver sections. The remaining animals were anesthetized from 1 to 16 times for periods of 10, 20, or 30 minutes every third day, after which liver sections were also obtained. The only significant difference between the control liver sections and those obtained from the vinethene-anesthetized animals was increased activity of the von Kupffer cells in some of the anesthetized animals. These results were quite different from those found when the dog was used as the experimental animal.

After 7 dogs in the cardiac series died in their pens 24 to 48 hours following anesthetizations given at least 3 days apart, a controlled pathologic study of vinethene toxicity was begun. On these dogs liver biopsies were obtained at the first anesthetization for control sections. Additional periods of vinethene of various duration and at various intervals were given, then samples obtained again at biopsy or post mortem. Table 4 shows the results. No abnormality was evident in any of the control sections. Of the animals given vinethene for 30-minute periods none showed any pathologic effects at the end of a week, but at the end of the second week degeneration was present. These administrations were by open drop technique, as recommended by the Council on Pharmacy and Chemistry of the American Medical Association in its acceptance of vinethene (6).

There was marked liver involvement after 3 anesthetizations in the animals receiving vinethene for an hour each week. These administrations were with approximately 88 per cent. of oxygen in addition to the required vinethene. The terminal picture and pertinent post mortem findings for dog E are:

> In great respiratory difficulties last 2 days, very weak, unable to move hind legs, unsuccessful in attempts to drink water. Anuria existed for the 2 days ante mortem. Bleeding time prolonged to 10–12 minutes.

TABLE 4

PATHOLOGIC FINDINGS IN DOGS AFTER VINETHENE ANESTHETIZATIONS. ADMINISTRATION OF VINETHENE AS DESCRIBED IN TEXT

Animal	Vinethene Anesthetizations			Liver Pathology	Other Pathology	Remarks
	Number of Administrations	Duration of Each Administration	Sequence of Administrations			
		min.				
III	1	60	Once	None	Not examined	Biopsy section normal. Killed 7 days after first administration
E	3	60	Every 7 days	Less extensive necrosis than B, C and D with some definite hepatic proliferation in attempts at regeneration	Kidneys—as for B, C and D Spleen—as for B, C and D	See text for typical post mortem findings (*) Weight change 17.1 to 15.1 kilograms
IV	3	60	Every 7 days	Central zonal necrosis	Not examined	Biopsy studies normal. Killed 7 days after last vinethene. Wt. change 9.5 to 7.8 kilo.
B	4	60	Every 7 days	Acute yellow atrophy	Kidney—albuminuria, moderately severe tubular cloudy swelling with obstruction and glomerular distention with membrane thickening and proliferation of cells of tufts Spleen—corpuscles atrophic, congestion edema, patchy necrosis with sinusoids standing out prominently	Died 2 days after fourth vinethene, death preceding by 3 hours that of litter mate C Post mortem findings as for E in text of paper
C	4	60	Every 7 days	Acute yellow atrophy, damage more severe than for litter mate B	Heart—necrosis of fibers, destruction of nuclei in wide areas. Other organs as for B.	Died 2 days after fourth vinethene, 3 hours after that of her litter mate B

TABLE 4—(*Continued*)

Animal	Vinethene Anesthetizations			Liver Pathology	Other Pathology	Remarks
	Number of Administrations	Duration of Each Administration	Sequence of Administrations			
		min.				
D	7	60	Every 7 days	Diffuse severe vacuolar degeneration	Kidney—more congestion, glomerular distention and cloudy swelling of tubules than B. Glomeruli show endothelial proliferation and early adhesions. Spleen—as for B and C	One week omitted in vinethene administration after third anesthetization
J	2	30	Every 3½ days	None	Not examined	Control biopsy normal. Biopsy at 5th day (after 1) and 8th day (after 2 anesthetizations)
K	5	30	Every 3½ days	None	Not examined	Control biopsy normal. Biopsy at 14th day (after 4) and 18th day (after 5 anesthetizations)
H	7	30	Daily	Normal except for marked cloudy swelling and slight atrophy at central areas	Kidney—cloudy swelling minimal, albuminuria pronounced	Biopsy control normal. Killed on 8th day. Weight change from 8.1 to 7.2 kilograms
G	14	30	Daily	Marked diffuse fatty degeneration, most marked in the central zones	Not examined	Control biopsy normal. Killed on 18th day. Weight change from 9.2 to 5.8 kilograms

Abdominal cavity contained ± 700 cc. of a thin, hemorrhagic fluid. Liver greatly congested, quite friable, with a marked greenish-yellow cast. Gall bladder greatly distended, containing 70–75 cc. reddish bile. Kidneys congested, differentiation and markings poor. Urinary bladder constricted into a solid muscular mass. Spleen distended. Mesenteric nodes enlarged and hemorrhagic. Petechial hemorrhages from duodenum downward over small and large intestine, particularly in the colon. Internally the G-I tract was coated with a pasty, bloody mucus from duodenum to rectum.

Lungs with pneumonic patches. Mediastinal nodes enlarged and hemorrhagic. Heart appeared normal.

These findings varied only in degree also for dogs B, C, and D. Figure 3 shows the central zonal necrosis commonly present and Fig. 4 is representative of the acute yellow atrophy found in dogs B and C.

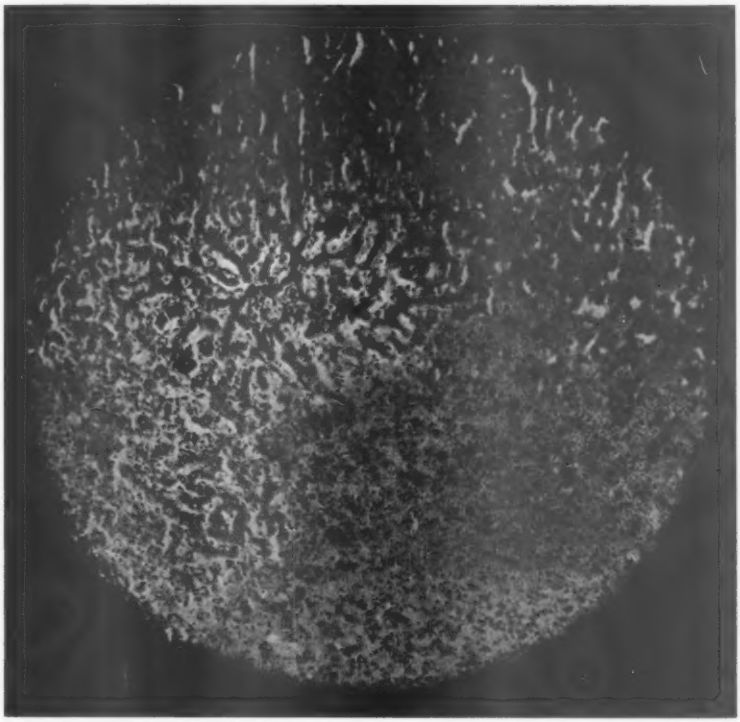

FIG. 3. Severe central zonal necrosis of the liver produced in dog E by one hour of vinethene anesthesia each week for three weeks.

Due to its known toxic action on the liver, chloroform was used for comparison with vinethene. After hourly anesthetizations of chloroform by open drop technique once weekly for 7 periods a biopsy re-

vealed a mild vacuolar degeneration. Administration was not continued since this was the greatest number of similarly given vinethene anesthetizations required to kill any animal.

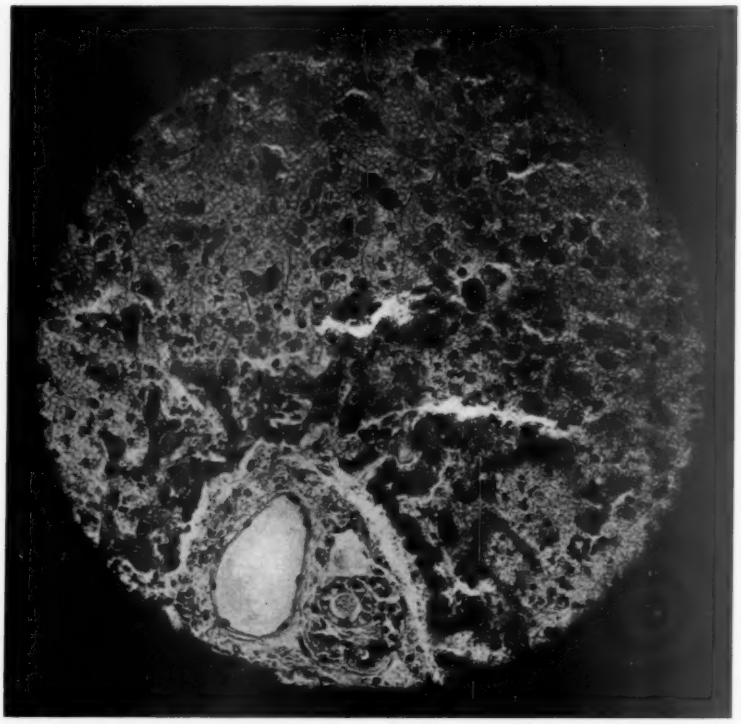

FIG. 4. Acute yellow atrophy of the liver produced by four vinethene administrations of one hour each at weekly intervals to dog B.

At the suggestion of Dr. Hans Moliter diethyl ether also was used for comparison. After control biopsies 2 animals were anesthetized for 6 one-hour periods at intervals of a week and biopsies taken again. No significant pathologic changes were found. In previous studies (2) 5 animals had received at least 5 ether and 4 chloroform anesthetizations each without any of the weight loss, depression, or other symptoms so obvious after only a few anesthetizations with vinethene.

DISCUSSION

From the results of tests with adrenalin, cobefrin, and neosynephrin during vinethene anesthetization it is evident that this agent does not seriously affect cardiac automaticity, in this respect being more similar to diethyl ether than chloroform or cyclopropane as previously studied

(1, 2). Failure of lower centers to be made automatic by the action of adrenalin on the heart is interpreted to mean a lack of sympathetic stimulation from higher centers, which has been demonstrated recently to occur with cyclopropane (7). As previously noted with cyclopropane, morphine-scopolamine premedication did not alter the automaticity of the heart significantly.

The marked reduction in the P-R interval with the accompanying average increase of almost 50 beats per minute in heart rate is explainable on the basis of inhibited vagal effects, such as is known to occur with diethyl ether. Decreases in QRS voltage and a similar change in the majority of cases with respect to the T wave may be indicative of some effects on the properties of conductivity and irritability in the myocardium and conducting system.

Anoxemia has been considered necessary before pathologic effects of vinethene occurred (8), and the delayed onset of hepatic damage when the agent was administered with high oxygen atmospheres has been noted (9). This led to our use of pure oxygen as a diluent. The routine employment of the carbon dioxide absorption technique, with endotracheal intubation providing for a patent airway, was considered a further safeguard against alteration of normal blood gases. With these precautions and adequate respiratory exchange, determinations of blood oxygen would not seem necessary but were done to prevent any explanation of the results as due to anoxemia. Routine duplicate analyses agreed within less than 0.5 volumes per cent. As a check on the technique of transfer to the modified Hempel pipette, control samples were analyzed by the routine method for blood oxygen as well as by the modified procedure.

That blood oxygen was adequate is indicated from Table 3. Only when the animals purposely were carried into the lower levels of surgical anesthesia in an attempt to abolish running movements or study blood pressure effects (dogs X and Y) was there a significant lowering of blood oxygen. This deep plane of anesthesia was never permitted in any routine experiment.

Due to the earlier disappearance of the running movements from the fore limbs, in contra-distinction to the accepted order of depression of the central nervous system in anesthesia, these movements were thought to be due to stimulation of lower centers or even to cord irritation. Their presence in all but one of the animals following separation of the cortex and basal ganglia from the cord, and their occurrence in the hind limbs of one of the animals with a complete cord transection at T-10, substantiate this opinion.

The possibility of these movements being caused by a breakdown of vinethene to related furan compounds seems quite possible, in view of the reports of the action of these substances by Johnston and by Henderson and Smith (10), (11).

As Burstein has shown there is a loss of intestinal tonus in all planes

of surgical anesthesia with vinethene (12). Our practically constant finding of a rise in gastric tonus was anticipated in view of the spontaneous flow of vomitus frequently observed during surgical anesthesia and often beginning 15 to 20 minutes after induction. Persistence of non-propulsive intestinal movements in the premedicated animals in light vinethene anesthesia corresponds to the results of Youmans et al. with cyclopropane (13). Absence of propulsive activity has not been reported previously.

Histologically the kidneys showed albuminuria, moderately severe cloudy swelling of the tubules, glomerular congestion, endothelial proliferation and early adhesions. It will be noted that in each of the 4 dogs on which urea clearances were determined there was a progressive decrease in kidney function after the first or second weekly period of an hour of vinethene. This is in marked contrast to cyclopropane, diethyl ether, and chloroform, which had been found not to alter kidney function (5). The clearances in dog F following chloroform did not differ essentially from the control values.

As previously reported by Molitor (14) liver damage after vinethene is not demonstrated in the rat. In our series of animals we likewise failed to find any effects with vinethene on this species. This seems explainable due to the marked power of regeneration of the liver in this animal.

Our controlled pathologic studies on the dog agree with the observations of Goldschmidt et al. (15) that there is a minimal duration of vinethene anesthesia necessary to elicit liver damage. This is evident from the lack of any severe effects with 7 daily administrations but fatty degeneration after 14 days. Since dog E died after 3 hourly periods at intervals of a week while dog D withstood this agent for 7 weeks before dying, it seems impossible to predict which animal will show an early response and which will be more resistant.

It is our belief that central zonal necrosis can be produced routinely by vinethene administration. It has been proved that this effect is not due to anoxemia. Since 7 anesthetizations with chloroform caused only mild vacuolar degeneration of the liver in one animal and since the 5 other dogs subjected to numerous diethyl ether and chloroform anesthetizations administered by the same technique and to the same depth of anesthesia showed no ill effects, the more marked pathology following vinethene is attributed to the greater toxicity of this agent.

There have been reported 5 clinical post mortems following the use of vinethene, 3 of which showed liver damage (15), (16). Each author has discounted the responsibility of vinethene for such pathology. In the two cases with liver damage reported by Goldschmidt et al. one subject received only 1 hour and 39 minutes, and the other 2 hours and 40 minutes of vinethene. In a later publication by the same workers it is stated, "There have been no instances of liver necrosis in the entire series" (17). It would seem that such a conclusion was in error. With

a new agent every blame should be placed on it until it has been proved definitely *not* to be responsible.

SUMMARY

1. Vinethene does not significantly affect cardiac automaticity in the dog, as tested with equivalent blood pressure-raising doses of adrenalin, cobefrin, and neosynephrin.

2. Anoxemia did not occur in the planes of surgical anesthesia routinely used in this study.

3. Aberrant twitches to running movements occurred in all vinethene anesthetizations. It is believed that they are due to stimulation of the central nervous system below the level of the corpora quadrigemina. In the majority of instances they were prevented by premedication with morphine-scopolamine.

4. Vinethene causes increased gastric and decreased intestinal tonus. Propulsive and non-propulsive movements of the jejunum are inhibited by surgical vinethene anesthesia.

5. Vinethene caused a progressive decrease in kidney function as measured by urea clearances.

6. In the dog vinethene has been found to produce central zonal necrosis of the liver and to be more toxic in this respect than chloroform. From post mortem reports in the literature it is suggested that a similar relationship exists in the human.

We wish to thank the Department of Pathology for inspection and confirmation of diagnoses of the histologic sections.

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SCIENTIFIC PROGRAM OF REGULAR MEETING OF THE AMERICAN SOCIETY OF ANESTHETISTS

745 FIFTH AVENUE, NEW YORK CITY

December 12, 1940—8 P.M.

1. The Fire and Explosion Hazard in Anesthesia: Report of a Clinical Investigation Based on Known Cases—30 minutes.

   By

   Barnett A. Greene, M.D., Chairman, Committee on Anesthetic Hazards. Director, Department of Anesthesia, Prospect Heights Hospital, Brooklyn, New York.

2. The Elimination of Explosive Anesthetic Mixtures by the Addition of Helium (Demonstration)—40 minutes.

   By

   George J. Thomas, M.D. and G. W. Jones (by invitation), Bureau of Mines, Pittsburgh, Pennsylvania.

3. A Report of the Committee on Hospital Research—50 minutes.

   By

   Professor J. Warren Horton (by invitation), Massachusetts Institute of Technology. Discussion to be opened by Everett A. Tyler, M.D., Philadelphia, Pennsylvania and H. Sidney Newcomer, M.D. (by invitation), New York City.

MENTAL DISTURBANCES FOLLOWING NITROUS OXIDE ANESTHESIA *

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AND

CYRIL B. COURVILLE, M.D.

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THE development of a psychosis after a surgical operation, while fortunately not of common occurrence, is now recognized to be one of the important complications of surgery. When this eventuality does occur, it is of primary interest to determine whether the mental symptoms are due to the surgical lesion or its complications, to the shock of the operation itself, or to the technic or agent used in inducting anesthesia. In many cases, certain predisposing tendencies are held to be responsible for the sudden appearance of such symptoms, particularly when there is a history of mental disease in other members of the family or of previous psychotic episodes in the patient himself. Aside from the presence of certain metabolic or toxic disorders, such as diabetes, thyrotoxicosis and primary anemia, the current disease is seldom to be reckoned as the cause of such symptoms. Even in the so-called "postanesthesia psychoses," the anesthetic agent is rarely ever held to be responsible for the mental aberrations.

In this study, the writers' purpose to establish the existence of a true post-anesthetic psychosis in which the various mental and emotional manifestations are consequent to nitrous oxide anesthesia, due to the asphyxial effect of this gas on the cerebral cortex and the lenticular nucleus. A survey of available literature has brought to light eleven well-defined cases. The writers' observations in ten additional cases lead them to believe that mental disturbances may occur more frequently after nitrous oxide anesthesia than has been generally supposed. It is hoped that this study may accentuate interest in the problem, particularly on the part of anesthetists, as well as psychiatrists, who must see a number of patients in larger institutions for the insane who survive with mental defects the anoxemic episode.

POSTANESTHETIC VERSUS POSTOPERATIVE PSYCHOSIS

Patients who develop symptoms of abnormal mental reaction after operation may be divided into two general groups. In the first group,

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the symptoms develop immediately upon recovery from a general anesthetic or at times while the patient is still partially under the influence of a spinal or local anesthetic. This group constitutes the class of *true postanesthetic psychoses.* In the second group the psychotic manifestations often appear several days after the operation. These cases are designated as instances of postoperative (or "interval") *psychosis.* The latent interval between recovery from the anesthetic and the onset of mental symptoms seems to preclude any possible etiologic relationship to the anesthetic agent. In this second group of cases, certain predisposing tendencies as well as factors contingent upon the operation, such as emotional and physical shock, hemorrhage and infection, play an important causative role.*

In the present study, the writers are concerned with the anesthetic agent, nitrous oxide, alone, as the prime factor in producing the psychosis and so no further attention will be given to the postoperative psychoses and their causes.

NITROUS OXIDE AND POSTANESTHETIC PSYCHOSIS

Nitrous oxide has long been known for its exhilarating effects incident to the minor degree of intoxication which it produces. Because of this effect, it has been designated by laymen as "laughing gas." Characteristic symptoms were undoubtedly seen more often when the crude gas was inhaled primarily for its stimulating effects, the resultant symptoms resembling those of mild alcoholism (1). In the early days of its use as an anesthetic, when a less pure gas was used without addition of oxygen under pressure, variable degrees and types of emotional and mental aberrations were described. Hewitt (2), one of the pioneers in the development of nitrous oxide-oxygen anesthesia, observed hysterical outbursts, hallucinations or cataleptic states, protracted stupor or frank insanity following use of this agent.

A number of cases of psychosis following the use of nitrous oxide have been reported in the literature. Perhaps the earliest recorded case is that of Savage (3) whose patient, a young woman given to overindulgence of alcohol, was at first delirious, then became frankly demented. The patient evidently did not recover. More recently Atkeisson (5) reported a case in which the patient became cyanosed and stopped breathing while under nitrous oxide-oxygen anesthesia. Spontaneous respiration was restored after a short interval after resorting to artificial respiration and the use of oxygen. The patient awakened

* Much has been written regarding the possible etiology of postsurgical psychoses. First of all, one must rule out a latent psychosis which the operation or complications of the surgical lesion provoke. Pre-existing toxic states such as alcoholism, uremia, morphinism, endocrine disorders as hyperthyroidism and diabetes may also be responsible. Emotional or physical shock and hemorrhage incident to operation or infection may also play important roles as etiologic factors. Soresi (M. J. & Rec. 122: 20 (July 1) 1925) goes as far as to indict mild drug addiction such as the habitual use of coffee, tea and tobacco as a cause in some instances. At any rate, no case of post-surgical psychosis can be correctly evaluated until hereditary and environmental factors, habits and pre-existing diseased states as well as the lesion at hand, have been considered as possible etiologic factors.

in a delirious state, was incoherent, mumbled to herself and cried continuously for twenty-four hours. She then lapsed into coma which, except for short intervals, was continuous until the time of her death forty-four days after anesthesia. A coroner's autopsy was done but the cranial contents were not examined.

Caine (6) described four cases with unusual complications of nitrous oxide anesthesia. One of his patients was " mentally hazy " for four to six hours after recovery from respiratory failure while under nitrous oxide anesthesia. This patient ultimately lost interest in life and died two months after anesthesia and after a progressively downward course. In Clement's first case (7), a child of seven remained unconscious after the mask was removed. After a short interval (five to ten minutes) the child began to toss about with a peculiar, wild-eyed and staring expression which continued for half an hour. Recovery was complete after a period of sleep. In Clement's third case, a four year old child was mentally cloudy for the rest of the day after nitrous oxide anesthesia. It had fully recovered by the next day. Doyle (8) described a case from the Mayo Clinic, a patient who became cyanosed and developed respiratory failure four minutes after nitrous oxide anesthesia had been started. The patient remained comatose after spontaneous respiration had been restored. She improved gradually but remained in a restless stupor for twelve hours. She was described as being normal the following day.

In a case described by Yaskin (9), a young woman of twenty-three years failed to regain consciousness after light nitrous oxide-oxygen anesthesia during delivery. She became partially conscious, screaming at intervals without apparent cause. During the next three or four days, she apparently improved although retrograde amnesia and emotional outbursts were evident. Recovery was not complete at the time the case was reported. In Case four of the series of Lowenberg, Waggoner and Zbinden (10), the patient was at first restless and noisy, then irrational for a day after nitrous oxide anesthesia. She improved during the next eight days but was still confused at times. She became oriented and emotionally stable within two weeks after anesthesia. In the case of Ford, Walsh and Jarvis (11), apathy, disorientation, poor memory for recent events, inattention and mental confusion were reported.

Steegmann (12) reported two cases with mental symptoms after nitrous oxide anesthesia. The first patient, a man of twenty years who survived for twelve days, presented a cloudy sensorium and emotional imbalance suggestive of hysteria. The second patient (13), a woman of thirty-one years, died sixteen months after an asphyxial episode. She showed a maniacal behavior, first interpreted as hysteria, but which persisted throughout her survival period as did facial grimacing and manifestations of decerebrate rigidity.

To these reports which have come to our attention, the writers wish to add their own observations. Judging from our experience, transitory to persistent mental changes after nitrous oxide-oxygen anesthesia are more common than is usually suspected.*

REPORT OF CASES

In the following series of cases which have come to the attention of the writers, particular attention is directed to the mental disturbances other than coma. Since coma or stupor is invariably present in all of these cases as a prolonged effect of the anesthetic any detailed discussion of this symptom seems quite superfluous. Emphasis will be placed rather on the more active manifestations of a disturbed sensorium.

Case 1.† A white man, aged 27 years, known to be a periodic drinker and to have indulged in alcohol as a "bracer" before going to his dentist, had several teeth extracted under nitrous oxide-oxygen anesthesia. After 40 minutes of anesthesia, respirations abruptly ceased and the pulse became imperceptible. After vigorous artificial respiration, spontaneous breathing was resumed. When seen one hour later by Dr. Louis B. Baldwin, medical consultant, the patient was comatose, the respirations were shallow and at intervals peculiar convulsive phenomena were in evidence.

The patient remained in coma for about 24 hours when a state of restless delirium developed. The speech was slow and hesitant and at times somewhat slurred. He remained in a state of mental confusion for two days when he became more rational and cooperative. The following day he appeared to be entirely lucid although purposeless movements of the extremities persisted. The following day he again became lethargic. During the remaining days of his life the patient was either irrational or completely comatose. He died 26 days after administration of the anesthetic.

The well-fixed brain was brought to the Cajal Laboratory by Dr. Carl W. Rand who knew of the interest of one of us (C. B. C.) in the subject. Grossly, there was a thickening and opacity of the arachnoid, unusual in degree for a patient of this age. On section the cortex appeared thin and granular, particularly on the medical aspects of the occipital lobes. Here the markedly attenuated cortex had a yellowish color. The lenticular nuclei were almost completely necrosed.

Histologically, variable degrees of degeneration of the cortex were noted either in the form of circumscribed astrovascular scars up to subtotal destruction of the cellular layers. The meninges showed cellular proliferations, the small superficial blood vessels at times showing deposits of calcium, or were enveloped by collections of lymphocytes. The central portions of the lenticular nuclei were also replaced by a vascular scar.

* A resident physician in an insane asylum told one of us (C. T. B.) that he recalled several cases admitted to the institution as insane following nitrous oxide anesthesia. Unfortunately there was no way in which these cases could be traced. No doubt there are a number of inmates in institutions in this country and other countries whose condition is to be ascribed to anoxemia.

† This case and Cases 2, 3, 4, and 5 have previously been reported in an article dealing with the asphyxial manifestation of nitrous oxide anesthesia as a whole (14). In this connection special stress will be laid on the mental disturbances only. For other details the original article may be consulted.

Comment.—This case was most unusual in that death occurred after a rather long interval following severe anoxemia under nitrous oxide anesthesia. The possible connection between alcoholism and the anoxemic episode is also of interest. We were unusually fortunate in having the privilege of studying the tissues histologically, the detailed changes being described in the original study.

Case 2 (15). A woman of 37 years was operated upon for chronic cholecystitis on Aug. 13, 1937. Anesthesia was induced and carried on for fifteen minutes by nitrous oxide and oxygen. A change was then made to ethylene-oxygen-ether because of marked cyanosis which persisted for several minutes in spite of a progressive increase in the oxygen content of the gas. Respirations were irregular during the remaining portion of the period of anesthesia.

The patient was comatose for a period of two days after which she regained consciousness, complaining that objects appeared hazy to her. It was also noticed that she was markedly reticent in speech; ordinarily she was quite voluble.

The patient remained mentally clear until Sept. 7, 1937, when she began to complain of frontal headaches and a feeling of faintness. She did not seem to understand what was said to her and answered all questions slowly. She was disoriented as to time. Control of the sphincters was lost.

This state of mental confusion persisted until three days before death. She paid very little attention to her surroundings or attendants. On September 25, she improved sufficiently to sit up in bed and read although she refused to talk to anyone. After a few hours she again lapsed into coma and died on Sept. 28, 1937, 46 days after anesthesia.

On examination of the brain by one of us (C. B. C.) the arachnoid was found to be slightly thickened, the cortex was thinned and, in the globus pallidus of both sides, an area of necrosis was found. The softened area presented a yellowish coloration. Histologically, aside from a slight friability of the cortex in the calcarine area, no other foci of cortical necrosis were discovered.

Comment.—This case is one of unusual interest in that recurrent periods of mental confusion constituted the most striking psychotic manifestation although negativism (reticence or frank refusal to talk) was also present throughout the postanesthetic course. The essential lesion as found at autopsy was a bilateral necrosis of the globus pallidus.

Case 3. A 30 year old white woman was admitted to the Obstetrical service of Dr. Lyle G. McNeile, at the Los Angeles County Hospital in a state of shock on August 21, 1931. A diagnosis of ectopic pregnancy with rupture of the Fallopian tubes was made and exploration was done about four hours after admission under nitrous oxide-oxygen anesthesia. Just as the abdomen was being opened, respirations suddenly ceased and were restored only after a period of 10 to 12 minutes of artificial respiration. During the remainder of the operation, the respiratory movements were strong and regular, but the pulse was feeble and irregular. Within half an hour after withdrawal of the mask, the surgeon noted a peculiar twitching of the facial muscles, marked nystagmus and a slurred speech.

The patient was examined by one of us (C. B .C.) some eight hours later, at which time she appeared stupid and apathetic. The pupils were small, equal and

reacted to light. The extremities were in more or less constant, jerking, purposeless motion. The deep reflexes were universally diminished and no inequalities were noted. Bilateral Babinski and Chaddock reflexes were elicited.

The patient's mental condition improved somewhat, although she remained apathetic and was at times stuporous. There was considerable drooling of saliva. The involuntary movements became less marked and the deep reflexes gradually became universally hyperactive with increasing rigidity of the extremities. There were periods of involuntary crying. The patient responded slowly to requests or questions. She was incontinent of urine. Irregularities of vasomotor control were observed with periods of coldness and moistness of the skin. The spinal fluid was found to be clear and colorless and chemically and serologically negative. The blood chemistry was normal. Her physical condition was gradually improved to the point where she was able to be discharged, although she was still mentally confused and emotionally disturbed; the extremities were still very rigid. She left the hospital in a wheel chair on September 28, 1931.

The patient was readmitted to the psychopathic ward of the hospital on March 22, 1932. It was learned that in the interval she had continued to be mentally disturbed, mumbled to herself and talked but little. She acted quite silly and cried easily. She seemed to comprehend what was said to her and attempted to reply but was unable to formulate sentences.

At the time of examination she presented a blank facial expression, smiled in a simple manner and acted rather childishly. Athetoid movements were present, the extremities were rigid, although at times she seemed able to relax. She was inclined to pull and pick at her clothing. All involuntary movements were slowly performed. When she walked it was with a wide base in an unsteady manner with her clenched hands held above her head or clapped together in front of her. She was able to carry out simple orders. A fine tremor of the tongue and fingers was present. The pupils were widely dilated, reacted to light and accommodation and the fundi were normal. The deep reflexes were universally hyperactive and spastic, a bilateral Babinski and Gordon were found, better developed on the left.

During her stay on the psychopathic service, what were considered to be catatonic states were observed. Because of the degree of dementia and physical helplessness she was committed to the Norwalk State Hospital for the insane.

She was seen at this institution by one of us (C. T. B.) over two years after her commitment. An advanced degree of rigidity was present in all extremities but apparently more in the arms. Mental deterioration had progressed to a degree of almost complete dementia, although her physical condition was good. The patient was seen again (C. B. C.) seven years after the asphyxial episode. There seemed to have been some recovery but the mental defect was still marked.

Comment.—This patient who had been perfectly normal mentally before admission to the hospital, developed a marked degree of dementia which was to be traced directly to a period of anoxemia under nitrous oxide anesthesia. The mental defect was associated with an advanced stage of parkinsonism indicating serious damage to the lenticular nuclei. Similar cases to this one must almost certainly be under observation in many other institutions for the insane.

Case 4.* A 19 year old Negro girl was admitted to the Los Angeles County Hospital in February, 1924. An appendectomy was done under nitrous oxide-oxygen anesthesia. She learned later (the hospital record not being available for exact details) that she had remained in coma for three days with generalized convulsions. She remained blind for a period of three months and was unable to make herself understood for six months. After being discharged, the girl developed purposeless movements of the extremities which became so rigid and contracted that she was unable to walk or assist herself to any great extent.

She was admitted again to the hospital on September 5, 1932, eight years later, with the complaint of pain in the lower abdomen and vaginal bleeding. Because of athetoid movements and childish mental reaction, the intern asked for neurologic consultation. The history of the anoxemic episode while under nitrous oxide anesthesia was then elicited. At this time, the patient presented a rather idiotic facial expression and her mental reactions were those of a 10 year old girl. She was easily amused and episodes of involuntary laughter frequently occurred. Her memory was apparently good, although answers to questions were hesitant owing to the drawling speech. No delusions or hallucinations were noted. There were characteristic athetoid movements in all extremities but particularly in the upper pair. The lower extremities were in extreme flexion deformity. All extremities showed marked spasticity.

This patient was seen again in September, 1935, when her mental status was again noted. No marked emotional outbursts were observed although otherwise she was about the same as when seen three years before.

Comment.—This patient presented a picture somewhat similar to that in the first case, with mental symptoms and signs indicative of degeneration in the basal ganglia. She differed from the first patient in that the mental changes were not so pronounced and a picture of lenticular degeneration, including involuntary laughter rather than of parkinsonism, was presented. The case could well have been mistaken for one of Wilson's disease by one unacquainted with the history.

For the records in the following case, the authors are obliged to Dr. Harold R. Hoover, intern on the case.

Case 5.† A 28-year-old pregnant woman, at term, was admitted to the Huntington Memorial Hospital in Pasadena, California. In order to facilitate delivery, the cervical os was opened by Dursshens incisions under nitrous-oxygen anesthesia on August 24, 1937. A normal infant was delivered by low forceps. Delivery was followed by profuse hemorrhage. Only slight cyanosis was observed during the hour that the anesthetic was being administered.

About 15 minutes after the close of the operation, the patient had a severe generalized convulsion during which she bit her tongue. She remained in a deep stupor throughout the night and the following day. On the third day, the patient was found to be conscious but was unable to recognize her physicians. She could answer simple questions in a childish way after some delay. Facial grimaces were frequently observed.

* This case was Case 11 of the original study (14). The patient was subsequently examined and a further report made (16). Only the essential psychiatric aspects of the case are being stressed in this connection.

† This case was reported in full in a monograph by one of us on the effects of nitrous oxide anesthesia recently published (17).

From this mental state, the patient made continuous but slow improvement although when discharged from the hospital one month later the patient could not recall her pregnancy or delivery and did not recognize the baby as her own.

When seen by one of us (C. B. C.) on February 21, 1938, about six months after nitrous oxide-oxygen anesthesia, the patient presented a childish mental reaction, laughing at the slightest provocation. While she still complained of a defective memory, there was no evidence of disordered mental activities or trends and her mental capacity was apparently normal otherwise.

Comment.—In this case, prolonged mental impairment followed nitrous oxide-oxygen anesthesia without serious evidence of anoxemia during the period of anesthesia. When last seen the patient was definitely improved although her memory defect and childish mental attitude were still very much in evidence.

Case 6. A white woman, 27 years of age, was admitted at term to the Good Samaritan Hospital, Los Angeles, California. She was delivered of a normal child under nitrous oxide-oxygen anesthesia. After withdrawal of the mask she failed to regain consciousness and remembered nothing that occurred for a period of 35 hours thereafter. She learned subsequently that during this interval she was extremely talkative and repeatedly asked the same question ("Does the child have a hair lip or cleft palate?") within a few moments after she had been told by the nurse that the child was perfectly normal.

After regaining consciousness, blurring in the left visual field, thickness of speech, difficulty in swallowing, jerking movements of both arms and marked paresis of all four extremities were elicited and persisted for about a month.

During the next two or three months, ease of fatigability, emotional instability, a feeling of inadequacy (as the patient described it) in caring for her child ensued. She lost interest completely in her work, her social contacts, her music and was perfectly content to remain inactive at home. Her memory was poor and she had great difficulty in trying to concentrate.

When first seen by one of us (C. B. C.) almost three years later, she still was somewhat unstable emotionally, and, when fatigued, her hands were quite unsteady. Her interest in previous avocations had never entirely returned.

Comment.—This is the first case with persistent symptoms in which the subjective feelings of the patient during the interval of recovery have been satisfactorily elicited. The outstanding residuals were emotional instability (which the patient states is an exaggeration of her normal emotional reaction) and a loss of interest in her environment. This "flattening of the emotional curve" seems to be one of the persistent residual characteristics of the anoxemic state provoked by nitrous oxide-oxygen anesthesia.

Case 7. The patient, a Negro woman of 30 years, para III, had a precipitate delivery with consequent first degree laceration of the perineum. Nitrous oxide-oxygen-ether anesthesia was given for repair. After a short period of time, the respirations became labored and then ceased entirely. Breathing was reestablished within a few minutes upon administration of oxygen. She remained comatose, however, after removal of the mask, later developing generalized convulsions. She then became restless and a delirious state developed. She was

apprehensive and cried out in fright and tugged at her restraints when an attempt was made to elicit the deep reflexes. At other times she stared blankly at her attendants or gazed into space.

The patient's mental condition improved rapidly so that she soon became oriented and cooperative. Examination four days after the anoxemic episode found her to be perfectly rational although an apraxia of the right hand and a limitation of vision to the lower quadrants of the visual fields were still evident. When seen five weeks later in the postnatal clinic she appeared to be perfectly normal in every respect.

Comment.—In this case the period of respiratory failure was very short and this probably accounts for the lack of permanent mental symptoms. The delirious state after nitrous oxide anesthesia seems to be quite characteristic.

Case 8. A 28-year-old woman was admitted to the obstetrical service of Dr. Edmund Lazard at the Los Angeles County Hospital with the diagnosis of an incomplete abortion. A dilatation and curettage was done under nitrous oxide-oxygen anesthesia. The patient was cyanosed and rigid while under the anesthesia but no cardiac or respiratory irregularities were observed. Upon being lifted from the operating table, the patient began to scream in a hysterical manner and continued to do so until quieted with paraldehyde. When examined an hour after cessation of anesthesia she was in a state of restless stupor, characterized by purposeless movements of the extremities. She could not be aroused by painful stimuli. At times she would apparently arouse spontaneously from her stupor and gaze about, staring blankly into space, evidently oblivious of her surroundings and attendants. Later on in the day she became more quiet and, after a night's rest, seemed quite normal mentally. At the time of her discharge from the hospital, nine days after admission, she showed no residual symptoms.

Comment.—This case was somewhat unusual in that the early manifestations after anesthesia were mistaken for hysteria. The peculiar staring, silent gaze was observed in a number of reported cases and seems to be one of the immediate residual characteristics of the condition.

For the records of the following case, the writers are very much obliged to Dr. Carl L. Biorn, intern, and Dr. Kenneth H. Abbott, attending neurologist at the San Bernardino County Hospital.

Case 9. A white woman, aged 26, was admitted to the San Bernardino County Hospital on Mar. 7, 1939, complaining of excessive flow presumed to be due to an incomplete abortion. The patient was markedly anemic with a red blood count of 2,630,000 per c.mm. and a hemoglobin of 50 per cent. Four days later, after the temperature had receded, a dilatation and currettage was done under nitrous oxide-oxygen anesthesia.

The patient did not recover promptly when the mask was withdrawn. She was apparently conscious but appeared to be very dull, apparently unable to comprehend what was said to her. When spoken to, the patient would sit bolt upright in bed, staring wide eyed about her, and asked, "What? What?" in an idiotic manner. At other times she appeared very distressed mentally,

moaned and threshed her arms about in an aimless manner. After administration of oxygen by nasal catheter and a transfusion, the patient became quiet and spent a restful night.

The following morning she was somewhat obtuse mentally but was able to understand what was said to her and talked in a rational manner. She had a complete amnesia for the events of the day before. The remainder of the postanesthetic course was uneventful and the patient was perfectly normal mentally when discharged on Mar. 21, 1939.

Comment.—Cerebral anoxia in this case was apparently due to the superimposition of anoxic anoxemia which accompanies nitrous oxide-oxygen anesthesia upon an anemic anoxemia incident to profuse hemorrhage. Fortunately the cortical insult was minor and the effects transitory.

Case 10. A Mexican boy of 5 years had 8 carious teeth removed under nitrous oxide-oxygen anesthesia on Mar. 2, 1939. He was not cyanotic at any time although once during anesthesia he caught his breath, suggestive of some minor respiratory difficulty. Because of oozing from the tooth sockets, it was deemed inadvisable to rouse him at once by forced oxygenation.

The boy slept for a period of 2 hours. When roused at the end of this period, he cried out in a hysterical manner. He did not recognize his mother, either visually or by the sound of her voice. When examined by one of us a little later, he was crying, incoherent and uncooperative. An advanced defect in both sight and hearing was evidently present.

By the following morning the child was found to have entirely recovered.

Comment.—This child is typical of a group of children who present untoward manifestations after nitrous oxide-oxygen anesthesia. While convulsions are perhaps more typically characteristic of the anoxemic state, mental changes are not uncommonly observed. For example, Clement (18) describes mental clouding in a child who shortly afterward recovered completely.

DISCUSSION

A survey of the reported cases and a study of those which have come under our own observation indicate that transitory, prolonged or even persistent mental disturbances may follow nitrous oxide-oxygen anesthesia. These phenomena have been known for many years. Hewitt (2) stated that hysterical outbursts, hallucinations, cataleptic states, protracted stupor or frank insanity has been observed. This wide variation in the type of mental symptoms is clearly evident from the reports of cases.

On the basis of type of mental disorder, the following classification of symptoms is suggested. *A.* Disturbances of consciousness: progressive coma in early fatalities, recurrent periods of coma in later fatalities and transitory coma in patients who partially or completely recover. *B.* Hysterical outbursts, followed by recovery, progressive dementia or fatal issue within a few days. *C.* Transitory emotional instability

may be followed by recovery or it may be more or less persistent and at times associated with poor memory. *D.* Hallucinatory states, often transitory. *E.* Delirium followed by complete recovery or by progressive dementia. *F.* Mental confusion, either transitory followed by complete recovery, or recurrent or persistent, resulting in fatal issue, often after an interval of days. *G.* Transitory or recurrent cataleptic states, the latter associated with progressive dementia. *H.* Progressive dementia, often with athetosis or generalized muscular rigidity.

It will be noted that in a number of cases more than one group of symptoms are present, disturbance of consciousness being followed by one or another of the other types of aberrations. Psychic changes are frequently associated with other neurologic manifestations, convulsions, muscular twitchings and carphologia in the period following anesthesia, spasticity and tremor (parkinsonian syndrome), athetoid or choreiform movements and visual disturbance in those who survive for an interval of days or weeks.

There is likewise considerable variation in the course of the symptoms. One state may follow another in progressive improvement. Improvement may indeed be very slow but progressive even months or years after the cortical insult. Somewhat more difficult to account for are the recurrent episodes which so often appear in patients who survive for an interval of days or even weeks. It is probably to be explained on the basis of vasomotor instability. It is about as difficult to explain either the rapid or slow progressive mental failure which has been observed in some cases after an interval of apparent recovery. It suggests some mechanism of destruction after partial recovery from the immediate asphyxial insult.

As shown by gross and histologic alterations in the cortex and basal nuclei (lenticular nucleus predominantly), persistent mental symptoms following nitrous oxide anesthesia are due to well defined organic change probably incident to asphyxia (19) and not to any preexisting hereditary or acquired mental trends. In addition to the production of focal, laminated or diffuse degeneration of the cortex or central necrosis of the lenticular nuclei, some abnormal physiological process is set up which permits recurrences of symptoms or favors a progressive course of the lesion, an unusual occurrence in what appears to be a degenerative lesion. This is perhaps to be accounted for upon an unstable vasomotor control in the damaged areas of the brain. The changes in the brain which occur in patients who survive for short intervals have been described *in extenso* in another study (14). In patients who survive for a few days or weeks, focal astrovascular scars or diffuse subtotal destruction of the cortex in certain regions (especially in the region of the calcarine fissure) often associated with extensive necrosis of the lenticular nuclei (especially the globus pallidus), have also been described. Changes in the cortex, white matter and basal ganglia have

been described in the brains of patients who have survived for weeks or months the anoxemic episode under nitrous oxide-oxygen anesthesia.

SUMMARY AND CONCLUSIONS

Psychotic manifestations after nitrous oxide anesthesia constitute a true postanesthetic psychosis which is not to be confused with a postoperative psychosis of other etiology. A survey of eleven cases reported in the literature and ten cases studied by the writers form the basis of this report. The residual mental and emotional symptoms vary considerably as to their nature, severity and persistence. Disturbances of consciousness, as coma or stupor, are invariably present. This state is followed by delirium, transitory or recurrent hysterical outbursts, emotional instability, hallucinatory or cataleptic states or mental confusion. In patients who survive, progressive dementia has been reported although improvement even after weeks or months has also been observed.

Psychotic states may be (1) transitory and followed by more or less complete recovery, (2) recurrent, often resulting in more serious demented states or death, or (3) progressively downward leading to more or less complete dementia. After the period of anesthesia, irritative motor phenomena (convulsive muscular twitchings or carphalogia) often accompany the mental disturbances. In patients who survive for days or weeks or who live with persistent mental or emotional changes, signs indicative of lenticular damage (athetosis, choreiform movements and muscular rigidity) are commonly seen. Alcoholism seems to predispose to cortical damage, resulting in the development of serious, often persistent, nervous or mental states, possibly due to a preliminary interference with cellular respiration.

It is likely that cerebral and lenticular damage are due to the accompanying asphyxia (anoxic anoxemia) and not to the toxic effects of nitrous oxide itself. In patients who die within a few days or weeks, patchy necrosis or subtotal destruction of the cerebral cortex is found, often associated with necrosis of the lenticular nuclei. Similar but less extensive changes are found in the brain of individuals who survive for a longer interval.

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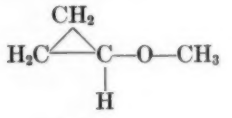
The Council on Scientific Assembly of the American Medical Association has announced the Officers of the new section of the Scientific Assembly of the Association to be called the Section on Anesthesiology. The appointments are as follows: Dr. Ralph M. Waters, Madison, Wisconsin, Chairman; Dr. T. J. Collier, Atlanta, Georgia, Vice Chairman, and Dr. John S. Lundy, Rochester, Minnesota, Secretary. Dr. John H. Evans, Buffalo, New York and Dr. Henry S. Ruth, Philadelphia, Pennsylvania, together with Dr. Waters as Chairman, were appointed to serve as members of the Executive Committee. Dr. Ruth was appointed to serve as a member of the House of Delegates of the Association representing the Section on Anesthesiology at the annual session to be held in Cleveland in 1941.

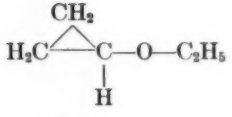
A meeting of the Special Affiliations Committees of the American Society of Anesthetists, Inc., and the International Anesthesia Research Society was held in Chicago, Monday, October 21, 1940, with the following entire membership present: E. A. Tyler and H. S. Ruth, Chairmen; E. Klaus, P. M. Wood, C. J. Wells and C. N. Chipman. The question of affiliation of the two societies was fully discussed. The two committees will again meet pending the final form of the amalgamation of the Associated Anesthetists of the United States and Canada and the International Anesthesia Research Society.

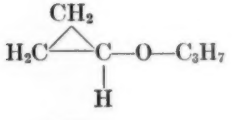
STUDIES WITH CYCLOPROPYL METHYL ETHER (CYPROME ETHER) IN MAN

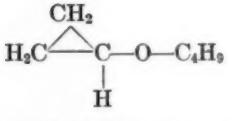
CONSTANCE BLACK, GEORGE E. SHANNON AND JOHN C. KRANTZ, JR.*

THE preëminence of ethyl ether among volatile anesthetics is uncontested. The introduction of ethylene to produce general anesthesia by Luckhardt (1) in 1923 marked the first substantial addition to the list of anesthetic agents in many decades. The development of a hybrid molecule between ethylene and diethyl ether occurred to Leake (2), the fulfillment of which resulted in the synthesis of divinyl ether by Ruigh and Major (3). In 1929 Lucas and Henderson (4) promulgated the use of cyclopropane, and after more than a decade of clinical trial its usefulness as a potent, valuable anesthetic agent is widely accepted. It occurred to one of the authors (J. C. K. Jr.) that it would be of interest from a chemotherapeutic standpoint to prepare a hybrid molecule between ether and cyclopropane. In addition, it was hoped that such a compound might augment the list of safe anesthetic agents. A synthesis was developed for the preparation of the homologous series of cyclopropyl aliphatic ethers, and the first four members of the series have been synthesized and identified. The structures of the compounds are shown by the following formulas:

(1)  cyclopropyl methyl ether (cyprome ether)

(2)  cyclopropyl ethyl ether

(3)  cyclopropyl propyl ether

(4)  cyclopropyl butyl ether

Only the first member of this series has been investigated pharmacologically (5) and is ready for clinical trial.

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Physical Properties

Cyprome ether is a colorless, mobile liquid, possessing an odor somewhat similar to that of cyclopropane. The specific gravity of cyprome ether is 0.786 25°/4° and the boiling range 43.5 to 44.0°. In the studies reported, cyprome ether gave a negative Beilstein test for halogens, contained no aldehyde and the total unsaturates present was less than 2 per cent. Cyprome ether dissolves in water to the extent of 5.5 gm. per 100 cc., while 6.2 gm. of ether dissolve in the same volume of water. The oil/water coefficient of cyprome ether is 6.7; that of ether is 4.5 (6). The vapor pressure at 26° C. of cyprome ether is 414 mm.; that of ether is 555 mm. (7).

The inflammability range of the vapor of cyprome ether (measured in an explosion pipette mixed with air or oxygen by exposure to the hot spark of an induction coil) is of the same order of magnitude as that of ether, namely, between 2 and 3 per cent.

Pharmacology

The union of the molecule of cyclopropane through an ether linkage with the alkyl radical, methyl, results in the formation of a volatile liquid possessing anesthetic properties in many species of animals. Cyprome ether is a more potent anesthetic agent than ethyl ether, although it is not so potent as chloroform. The concentration producing surgical anesthesia in the blood of the dog averages 0.10 per cent. Its anesthetic index as measured on the dog is 2.31; that of ethyl ether is 1.76. It should be emphasized that this difference arises mainly from the short induction period of cyprome ether compared with that of ethyl ether. These data are presented graphically in Fig. 1. In the monkey, cyprome ether produces no liver damage as shown by the bromsulfonphthalein test. In the rat histopathological changes are not found in the liver or kidneys after repeated anesthesias. The blood pressure remains high and the pulse good under deep surgical anesthesia in the dog with cyprome ether. Electrocardiographic studies in the monkey showed that cyprome ether (19 experiments) did not as a rule produce arrhythmias. In one animal a ventricular extrasystole was produced, but no definite tachycardia.

First Anesthesia in Man

The pharmacological studies on cyprome ether summarized in the foregoing paragraph warranted its use as a general anesthetic agent in man. A woman aged 55 years, a hospitalized patient, requiring an operation of short duration (rectal fistula) was selected with her consent for the first anesthesia. At 10:45 a.m. on Saturday, April 20, 1940, one of the authors (G. E. S.) began the administration of cyprome

ether by the drop method. At 10:49 a.m. surgical anesthesia was obtained. At 10:55 a.m. Dr. J. Herbert Wilkerson directed the discontinuing of the anesthetic agent. At 11:02 a.m. the patient responded

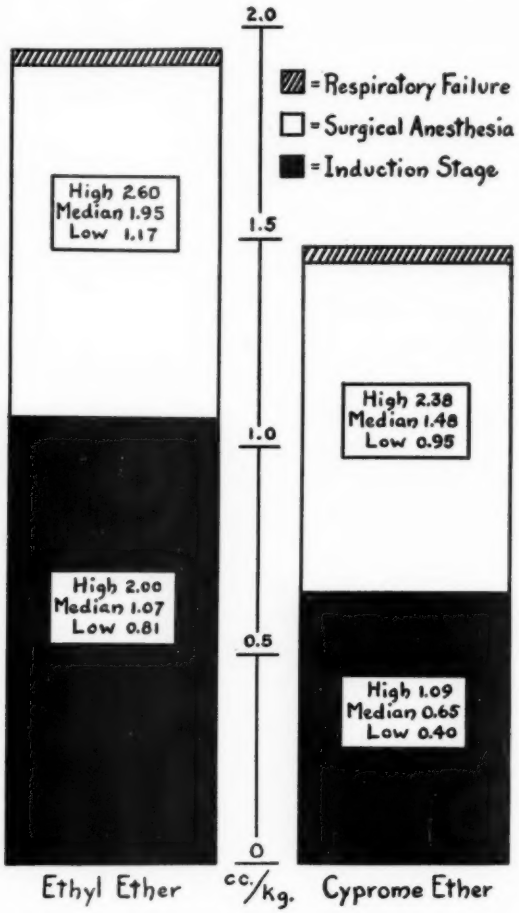

FIG. 1. Median values anesthetic index (Dog 45 experiments).

to the call of her name. Her recovery was uneventful. Blood-sugar level and N.P.N. were not significantly changed. The carbon dioxide combining power of the blood, one hour after anesthesia, was 50 volumes per cent. No control was available.

SUBSEQUENT ANESTHESIAS IN MAN

The authors wish to emphasize that this report of the first 25 cases of surgical anesthesia with cyprome ether is purported to convey only a first approximation of the value of this anesthetic agent in man. In these anesthesias the primary consideration was the safety of the patient and frequently complete relaxation was sacrificed to a lighter anesthetic plane, owing to the solicitude of the anesthetist. The cases, however, cover a large number of surgical procedures and serve to demonstrate the availability and safety of the new agent. The operations performed under cyprome ether anesthesia are listed:

Rectal	3
Tonsillectomies	5
Amputation	1
Reduction of Fractures	2
Abdominal	9
Herniotomies	2
Miscellaneous Minor	3

In this group the longest administration of cyprome ether was 90 minutes.

ANESTHETIC TECHNICS

Cyprome ether was administered by a variety of methods, e.g., open drop, open drop with oxygen added under mask, closed circuit induced by nitrous oxide and oxygen, and closed circuit with oxygen alone. The agent was administered with and without preoperative medication. The potency of cyprome ether as measured in laboratory animals appears to be greater than that of ethyl ether. This appears to hold also for man and is manifested by a shorter period of induction and a lesser amount of the agent required for a given anesthesia. In unpremedicated anesthesias in children, the open circuit method gave induction periods similar to those of ethyl ether, although it is believed that they were of shorter duration. The higher boiling point of cyprome ether lessens the amount of the anesthetic agent disseminated through the surrounding atmosphere during the induction period. Using the closed method, induction with nitrous oxide seemed preferable to that with cyprome ether alone, although there were several smooth inductions with cyprome ether alone. There appeared to be a tendency on the part of some of the patients to breath-holding during induction, possiblly owing to some laryngeal irritation. Laryngeal spasm was occasionally encountered.

RELAXATION DURING SURGICAL ANESTHESIA

In all of the foregoing anesthesias, relaxation of the abdominal musculature was comparable to that obtained during the same plane of ether anesthesia. In two abdominal operations where greater relaxation was desired and one of the authors (C. B.) hesitated to augment

the amount of cyprome ether in the respired air, owing to unfamiliarity with the agent, a small quantity of ethyl ether was added to increase abdominal relaxation. In later cases it was observed that relaxation was readily obtained with cyprome ether without producing untoward results.

Blood Pressure, Pulse and Respiration During Surgical Anesthesia

The data assembled on the twenty-five cases of surgical anesthesia with cyprome ether show that the blood pressure remains significantly unaffected during the anesthesia. The pulse is not usually affected in rate or volume. When the agent is pushed rapidly, producing the deeper plane of surgical anesthesia, an occasional arrhythmia is observed similar to that seen during cyclopropane anesthesia. The respiration is deep and regular under anesthesia and like ether, cyprome ether appears to be a mild reflex respiratory stimulant during the induction period.

Post Operative Sequelae

In a series of twenty-five cases it is impossible to draw any significant comparative conclusions with regard to postoperative sequelae. Many of the patients had no symptoms whatsoever. A few of the early patients complained of headache. Vomiting occurred in about one-third of the cases. Most of the cases were premedicated with morphine which many times vitiates any significance that may be attached to postoperative nausea.

Kidney function and liver function tests were not performed on these patients.

Potency

The pharmacology of cyprome ether in many species of animals showed it to be more potent than ether and to exhibit a much shorter induction period. The former was shown to obtain in man, as from ¼ to ½ the amount (measured by volume) of cyprome ether was required as would probably have been required of ethyl ether. Its potency permits a high concentration of oxygen in the respired air and hence the avoidance of hypoxia. At present there are too few cases to comment definitely on the relative time of induction periods in man.

Summary and Conclusions

1. Cyclopropyl methyl ether, so-called cyprome ether, which represents chemically a hybrid molecule between an aliphatic ether and cyclopropane, is an anesthetic agent in man, as has been shown previously (5) in many other species of animals.

2. Human beings under cyprome ether anesthesia appear to exhibit syndromes which are characterized by symptoms of both cyclopropane and ether anesthesias.

3. The authors refrain from drawing any conclusions with regard to the relative advantages or disadvantages of this anesthetic agent. That cyprome ether is less volatile (boils 9.5° C. higher) than ethyl ether and is more potent than ether are observed from the data assembled. The twenty-five human cases herein reported in conjunction with pharmacologic experiments indicate that cyprome ether in skilled hands is a safe anesthetic agent.

4. The authors wish to emphasize again that our knowledge of the action of this agent on man is still in its incipiency and our data are fragmentary; more work, which is in progress, will be necessary to establish the position merited by cyprome ether among the general anesthetic agents.

The authors are indebted to the Ohio Chemical and Manufacturing Co. for manufacturing and supplying to us generous samples of cyprome ether.

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Physician-anesthetists desiring certification should obtain information from the Committee on Fellowship of the American Society of Anesthetists, Inc., E. H. Eliasberg, M.D., Secretary, 275 Central Park West, New York City.

If the practice of physician-anesthetists is limited exclusively to the specialty, they may be eligible for certification by the American Board of Anesthesiology, Inc., Paul M. Wood, M.D., Secretary, 745 Fifth Avenue, New York City. It is suggested that possible applicants read the statement of the American Board of Anesthesiology, Inc., in the Journal of the American Medical Association, which statement is appearing in alternating current issues.

TOTAL SPINAL BLOCK: A PRELIMINARY REPORT *

CoTui, C. L. Burstein and W. F. Ruggiero

New York, N. Y.

One major difficulty in the study of spinal anesthesia induced by the classical method, i.e., by injection of the anesthetic drug through a lumbar puncture, is the inconsistency of its manifestations. When one analyzes the number of factors in this method not amenable to experimental control, this inconsistency is not surprising. Among these factors may be mentioned the speed of the spread of the drug along tubes of different lengths and calibres, the influence of body postures and curvatures on this spread, the mixing of the drug with the cerebrospinal fluid, the rate and quantity of fixation and gradual attenuation of the drug by the surrounding tissues and fluids, the effect of varying pressures of the cerebrospinal fluid on the spread of the drug, and the difference in the affinity of the drug between sensory and motor nerves.

Manifestations of the last factor may be demonstrated by cases where the sensory anesthesia extends to the level of the clavicle or even to the tongue and scalp while respiration persists. There is thus a lack of parallelism between the level of anesthesia and the level of motor nerve paralysis. Under such circumstances, then, observations made in one case of spinal anesthesia may differ materially from those made in another. The criterion of the level of sensory anesthesia of the skin surfaces, while reliable enough to determine relief of pain, cannot be used as an index for the phenomena which have for their basis the blockage of the motor pathways. It is precisely motor paralysis which gives rise to most of the undesirable complications.

In experimental work with the dog, these difficulties are even more exaggerated. This exaggeration is partly due to a number of factors peculiar to the anatomy of the dog. In this animal the spinal subarachnoid space is of almost capillary dimension, and the spinal curvatures are differently distributed and more acute than in man. It has been shown by one of us (CoTui) that in a tube of small calibre the gravity flow is retarded because of increased friction, and that the exaggerated curvatures of the dog's spine would serve to prevent an even spread of the drug by trapping the heavier anesthetic solution in the thoracic concavity (1). An attempt was made to overcome these difficulties by the use of large doses (400–800 mgm. procaine) (1, 2). With these amounts uniformity of results was secured but the very large size of the doses made the experiments open to doubt.

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In 1934 a technic of perfusing the spinal subarachnoid space of dogs with an anesthetic solution of suitable strength in order to secure simultaneous effect of the drug on the spinal nerves was described (2). In the present work this method has been used to induce a state in which the function of all the spinal nerves, motor as well as sensory, are almost simultaneously and uniformly affected. This state is termed Total Spinal Block (TSB).

EXPERIMENTAL PREPARATION

Dogs of from 15 to 18 kilograms and 55 to 65 cm. spinal length are narcotized with 70 mgm. of chloralosane per kilogram body weight given intravenously. The blood pressure curve is recorded on the kymogram by connecting a femoral or carotid artery to a mercury manometer. The respiratory record, when registered, is made by a lever connected with pneumographs strapped around the chest or abdomen. The atlanto-occipital membrane is exposed and opened, the opening made as large as possible to allow free drainage. A ureteral catheter is passed through the opening caudally in the subarachnoid space to the sacral region. The cerebrospinal fluid in the spinal subarachnoid space is then aspirated, or drained off. The head of the animal is lifted from the table in order to prevent the flow of the injected solution into the cephalic subarachnoid space, and the anesthetic solution, procaine hydrochloride 3–5 per cent., is injected with a syringe into the spinal subarachnoid space, through the catheter. The excess solution drains off freely through the opening in the atlanto-occipital membrane. From 4 to 8 cc. are usually required before overflow occurs. For reasons apparent in the latter part of this discussion, the lateral decubitus is the standard position used throughout the course of the work.

The advantages this preparation has for the study of phenomena associated with paralysis of the spinal motor nerves are the elimination from experimental consideration of the factors of slow spontaneous spread of the drug, the influence of factors of body curvatures on this spread, the long time required for the development of any uniformity of effect, and the absorption and destruction of the drug while the full picture is developing. Other advantages of the method are the small doses of the drug used (120–400 mgm.), the uniformity of the concentration of the drug affecting all somatic levels and the almost simultaneous exposure of the spinal nerves to the drug. The disadvantage of the preparation is its unsuitability for the study of the various phases of spinal anesthesia depending upon the hydrodynamics of a closed subarachnoid space, which has naturally been disturbed by tampering with the cisterna magna and the spinal subarachnoid space.

In the interpretation of the results, it must be cautioned that the picture presented by these preparations may not be that of all or most cases of spinal anesthesia. It should be taken as an extreme, or end-

point picture, short of medullary paralysis. Between this and the normal state, the spinal anesthetist must construct his pictures to fit the different degrees of motor involvement which he finds in practice.

SEQUENCE OF EVENTS IN TOTAL SPINAL BLOCK

The sequence of events following the induction of Total Spinal Block is illustrated in Fig. 1. A few seconds after the perfusion of the spinal subarachnoid space, there is an acceleration in pulse rate and a decrease in pulse pressure. This is followed by a slight decrease in the blood pressure. The respiratory excursions, both intercostal and diaphragmatic, are paralyzed almost simultaneously so that artificial respiration must be instituted immediately after the perfusion. The blood pressure falls progressively until the full establishment of the block when it reaches the minimum, 50 to 75 per cent. of the initial blood pressure. It remains at this level until recovery begins.

The pulse, instead of continuing to increase in rate with the fall of blood pressure, begins to slow 4 to 5 minutes after the perfusion. With full establishment of the block, the rate is usually markedly slower than the initial pulse rate. However, in cases where the drug is permitted to reach the base of the brain, there may be no bradycardia. This latter phenomenon is thought to be due to paralysis of the vagi as well as the cardio-accelerators, although the real mechanism has not been definitely determined.

The tendon reflexes of both the upper and the lower extremities are also almost simultaneously abolished. At the full establishment of the block, the only muscles contracting in response to artificially induced asphyxia are the muscles of the ears, jaws, and other muscles of the head (Fig. 7).

Recovery.—Paralysis begins to subside in 1 to 2 hours, depending upon the concentration of the drug used. The first sign of recovery is an increase in the pulse rate (Fig. 1, 4:20 strip), followed by a gradual rise in the blood pressure (Fig. 1, 4:40 strip). The respiratory muscles then begin to respond to asphyxia by twitching. Other muscles regain their twitching, which seems to be exaggerated by chloralosane. It requires forty to sixty minutes for the blood pressure to reach the initial level and at least two hours for the heart rate to regain the initial level. The recovery point is not sharp by any of these criteria. Strips 5:15 and 5:17, Fig. 1, show the different stages of recovery.

BEHAVIOR OF THE TOTAL SPINAL BLOCK ANIMAL UNDER STRESS

1. *Postural Changes*

A. Dorsal Decubitus.—With the blood pressure curve stabilized in the lateral decubitus, if the animal is now turned into the dorsal decubitus, the blood pressure falls promptly to shock level. Upon re-

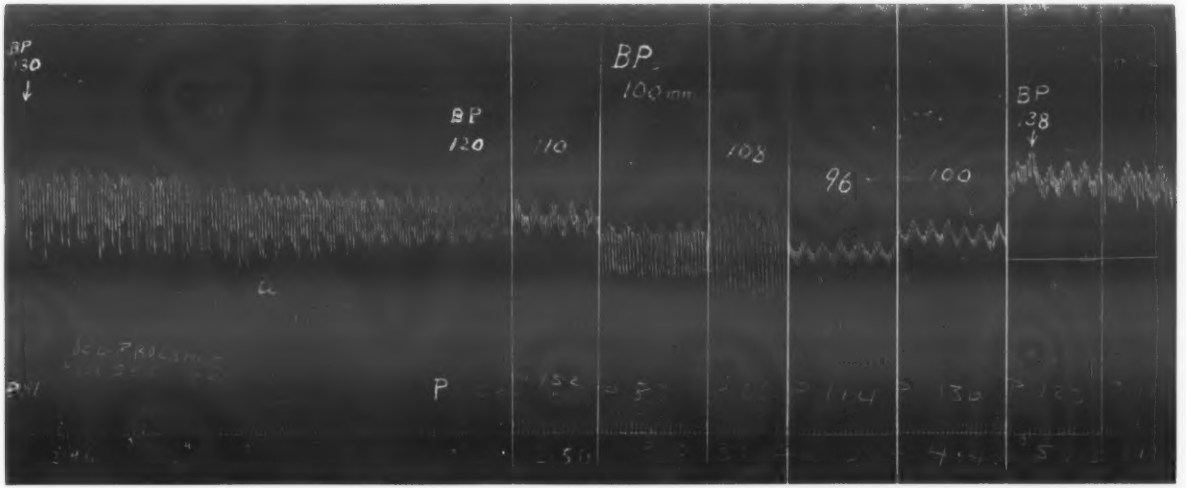

FIG. 1. Kymogram showing the course of total spinal shock.

Dog, Male, 17.5 kg., 70 mgm. chloralosane per kilogram body weight intravenously at 2:30. The atlanto-occipital membrane is exposed and the ureteral catheter introduced at 2:40. The animal is in the left lateral decubitus throughout the course of the experiment.

2:46 strip. Initial systolic blood pressure: 130 mm. Hg, pulse rate: 87. At 2:46 between the two marks, the spinal subarachnoid space is perfused with 6 cc. of a 5 per cent. solution of procaine-HCl. Note that beginning at "*a*" the pulse rate is accelerated and the pulse pressure decreased. At the end of the strip the systolic blood pressure has fallen to 120.

2:50. Note further acceleration of the pulse rate and further fall of the systolic blood pressure to 110 mm., with a mean pressure of 100 mm. Tendon reflexes are diminished.

3:07. The systolic blood pressure has fallen to 100 mm., the mean blood pressure to 87 mm., the pulse rate has returned to the original rate of 87. Tendon reflexes are now absent. This strip marks the beginning of the full establishment of TSB.

3:17. Note the reduction of the pulse rate to 69. Tendon reflexes are absent.

4:20. The systolic blood pressure is now 96, with a mean pressure of 88 and the beginning of an acceleration in pulse rate, which marks the beginning of recovery. Tendon reflexes are absent.

4:40. Pulse rate is now 130, and the systolic blood pressure 100 with a mean pressure of 96. Tendon reflexes returning but weak.

5:15. Systolic blood pressure now 138 mm. and the pulse rate is beginning to fall. Tendon reflexes active.

5:17. Note further fall in pulse rate.

The time marker in this and subsequent kymograms records seconds.

sumption of the lateral decubitus, there is a prompt return to the previous level. This phenomenon reported by one of us (C. L. B. (3)) is illustrated by Fig. 2.

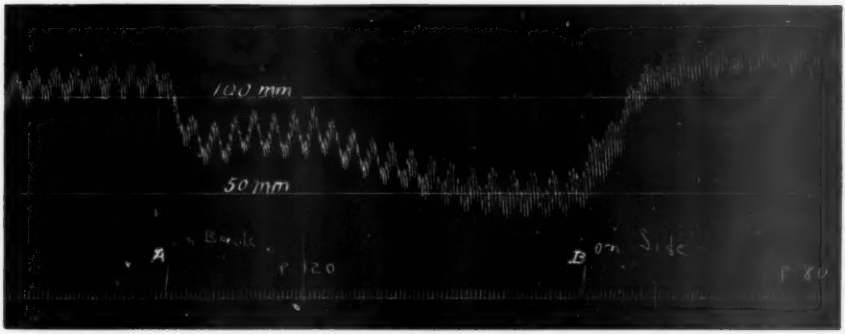

FIG. 2. Effect of Dorsal Decubitus on the blood pressure in TSB.

Dog 18 kg. TSB induced at 11:35. Note that the resulting systolic blood pressure is over 100 mm. Hg. At *"A"* the animal was turned from the left lateral to the dorsal decubitus. Note the precipitate fall of blood pressure to nearly 50 mm. At *"B"* the animal was returned to the left lateral decubitus. Note the prompt rise in blood pressure to above the level before the positional change.

A change from one lateral decubitus over an angle of 180° to the other does not occasion this fall, nor does the change from the lateral decubitus to the prone. In the preliminary report it was intimated that this phenomenon seemed to be related more to the position per se of the animal than to the motion of turning. Further work on the mechanism of this phenomenon to be published in extenso elsewhere indicates that it seems to have its basis on paralysis of the cardiac nerves.

In 1932 Bower, Clark, Wagoner and Burns (4) reported that when the spinal anesthetic drug reaches the 4th thoracic nerve roots, there is a dilatation of the heart as shown by myocardiographic tracings. To this cardiac dilatation they attribute the major part of the fall in blood pressure. The occurrence of the hypotension in the dorsal decubitus may well have the same basis as the effect reported by Bower et al. Since in their experiments the animals were in the dorsal decubitus (5), it would be interesting if hypotension associated with the cardiac dilatation, as reported, is present in the lateral decubitus.

B. Trendelenburg Position.—The response of the blood pressure curve when the animal is changed from the level position to the Trendelenburg is substantially the same in both the lateral and the dorsal decubitus. In either case, there is a slight rise in the blood pressure curve of a few seconds' duration, followed by a fall to the previous level or lower. Occasionally this slight rise is sustained. This response in TSB preparations is similar to that of the dogs in spinal anesthesia given by the lumbar method. This transient rise in the blood pressure

was interpreted as due to the gravity influx of blood from the elevated part of the body into the heart, thus temporarily increasing its output.

C. Head-Up Position (Reversed Trendelenburg).—With the animal in TSB, when the head of the table is raised, there is likewise a transient rise of blood pressure, followed by a fall below the previous level. In Fig. 3 is shown the blood pressure curve of a TSB dog raised into the

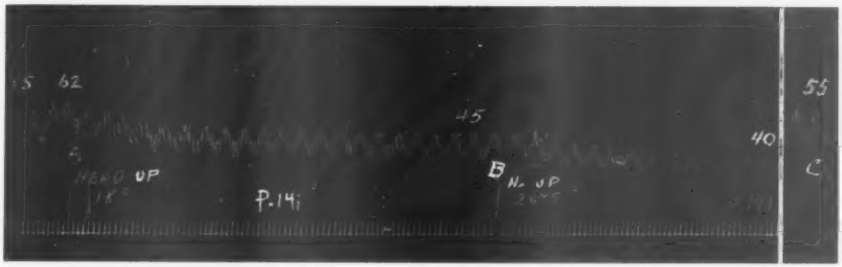

FIG. 3. Effect of "Head-up" position on the blood pressure in TSB.

Dog 15 kg., given 70 mgm. chloralosane per kilogram body weight intravenously. The spinal subarachnoid space was perfused at 3:00. The systolic blood pressure at 3:26 was 55 mm. Hg. Raising the foot of the table 18° at "*A*" caused the blood pressure to rise to 62, and then to fall to 45. Raising it further to 25.5° at "*B*" caused another slight rise and then a fall to 40. "*C*" shows the blood pressure stabilized again at 55 after the table was leveled.

head-up position in two stages, 18° and 25.5° above the horizontal. There is first a rise in blood pressure and then a fall. Thus in Fig. 3, the initial level was 55 mm., then a rise to 60 mm. immediately on assumption of the head-up position at "*A*," followed by a fall to 50 mm. When the table was raised to 25.5° (*B*), there was again a slight upward trend, and again by a fall to 35 mm. On levelling the table, however, the blood pressure rose to the original level.

D. Hemorrhage.—The response of the TSB animal to hemorrhage is shown in Figs. 4 and 5. It will be seen that the acute loss of 100 cc. of blood (.55 per cent. of body wt.) from a large artery in the normal animal, caused a temporary fall of systolic blood pressure from 138 mm. to 97 mm., a fall of 29.7 per cent. The upward trend of the blood pressure occurred two seconds after the bleeding stopped, and it required less than a minute to reach a stable level. There was marked acceleration of the heart rate, showing that the cardiac accelerators were active. After the retransfusion of the blood drawn, TSB was induced. At the height of the block, the same amount of blood lost caused the blood pressure to fall 40 per cent. from 70 mm. to 42 mm. and to stay at this level for a prolonged period. Even the retransfusion of the entire bled amount caused only a slight rise. The absence of cardiac acceleration is additional evidence of the absence of any homeostatic mechanism. Even in experiments in which the blood pressure at the height of the TSB is at the physiologic level, as in Fig. 5,

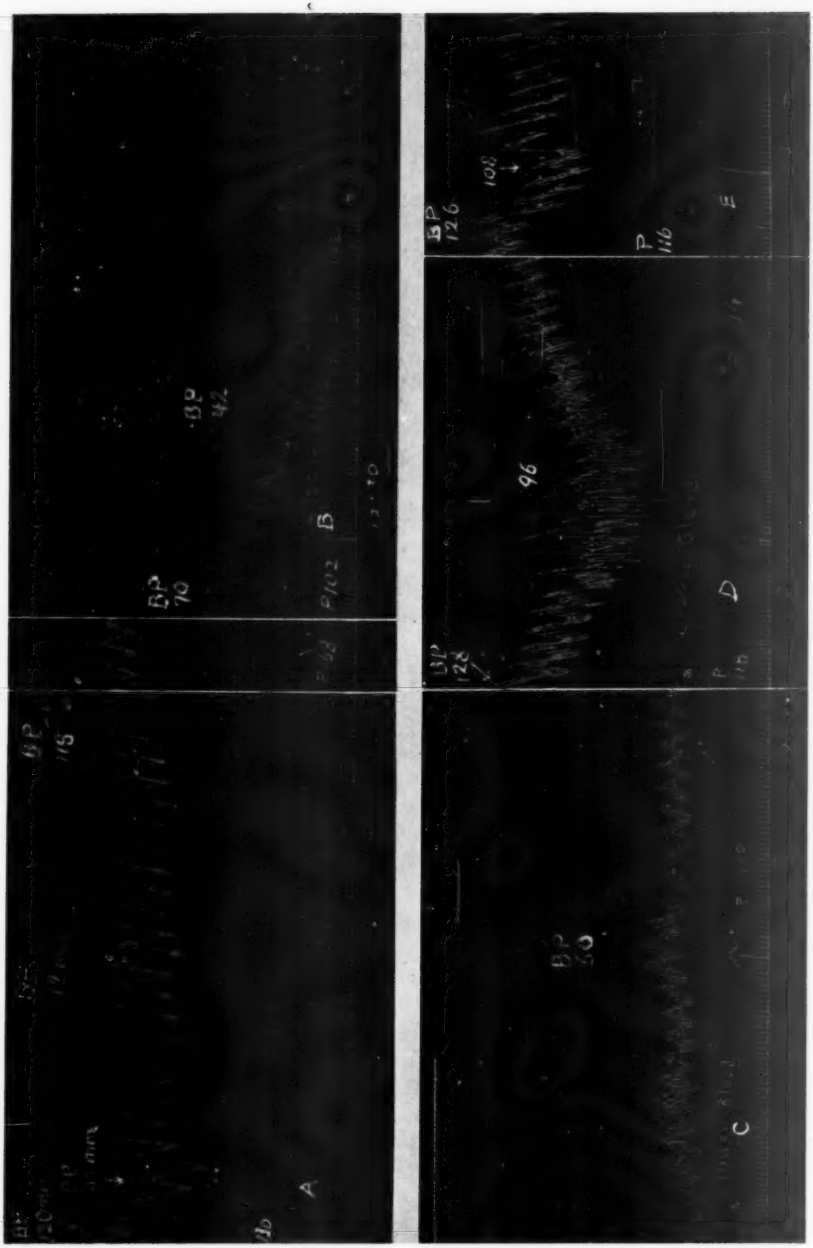

FIG. 4.

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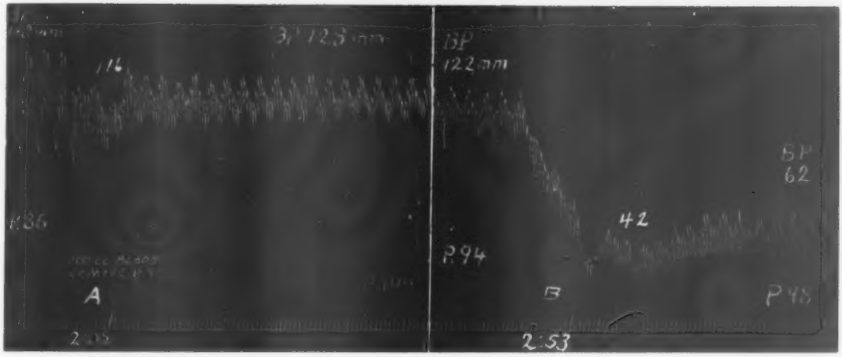

FIG. 5. Effect of bleeding.

Dog 18 kg. chloralosaned.

2:05 strip. Initial systolic blood pressure 140 mm., pulse rate 86. Bled 100 cc. at "*A*." Note the fall to 116 (only 17 per cent.). Note the prompt recovery, and the acceleration of the pulse rate to 105. The blood collected was retransfused at 2:20.

2:53 strip. TSB was induced at 2:40. Note that the blood pressure after the induction of TSB was 122 mm. Hg. The bleeding of 100 cc. at "*B*" caused a sharp dip in blood pressure to 42 (70 per cent. fall). Note that there was practically no attempt at recovery.

this marked fall in response to comparatively slight blood loss and the failure of the heart to accelerate are present.

In this connection it is interesting to recall the experiment of Burch, Harrison and Blalock (6) (1930) who found that dogs die from hemorrhage much more readily during spinal anesthesia than normal dogs; from .8 to 1.8 per cent. of body weight in blood being the lethal amount, while normal dogs do not reach a state of severe shock until from 3–4 per cent. of body weight of blood is lost.

FIG. 4. Effect of hemorrhage.

Dog 18 kg.—70 mgm. chloralosane intravenously at 11:30.

12:10 strip—initial systolic blood pressure—120 mm. Hg, pulse rate 130 per minute. The bleeding of 100 cc. from the right femoral artery at "*A*" caused the blood pressure to fall temporarily to 97 from which there was a prompt recovery, after the bleeding stopped. Note that the upward trend occurred in 2–3 seconds. Also note the acceleration in the pulse rate to 152, and to 168 on the 12:15 strip.

Between the 12:15 and the 12:30 strips, the blood collected in 5 per cent. sodium citrate was retransfused into the dog. TSB was induced at 12:18.

12:30 strip. The TSB blood pressure was 70 mm. Hg, the pulse rate 120. At "*B*," 100 cc. of blood was again removed. Note the prolonged fall of blood pressure to 42, without any attempt at recovery. Note also that the pulse rate did not increase, showing the lack of cardiac sympathetic action.

12:35. The blood was retransfused with but a slight rise of blood pressure to almost 60 mm.

2:30. Partial recovery from TSB. Blood pressure now 128, pulse rate 118. Blood 100 cc. at "*D*," both respiration and tendon reflexes had recovered and the hypotension of dorsal decubitus was now absent. Blood pressure has fallen to 96 as a result of the bleeding. Note prompter recovery, which is still delayed when compared with 12:10 strip.

Between 2:30 and 3:10 strips blood collected at 2:39 was retransfused.

3:10 strip. Blood pressure now 126. Bled 100 cc. at "*E*." Note the prompt recovery comparable with that in 12:10 strip.

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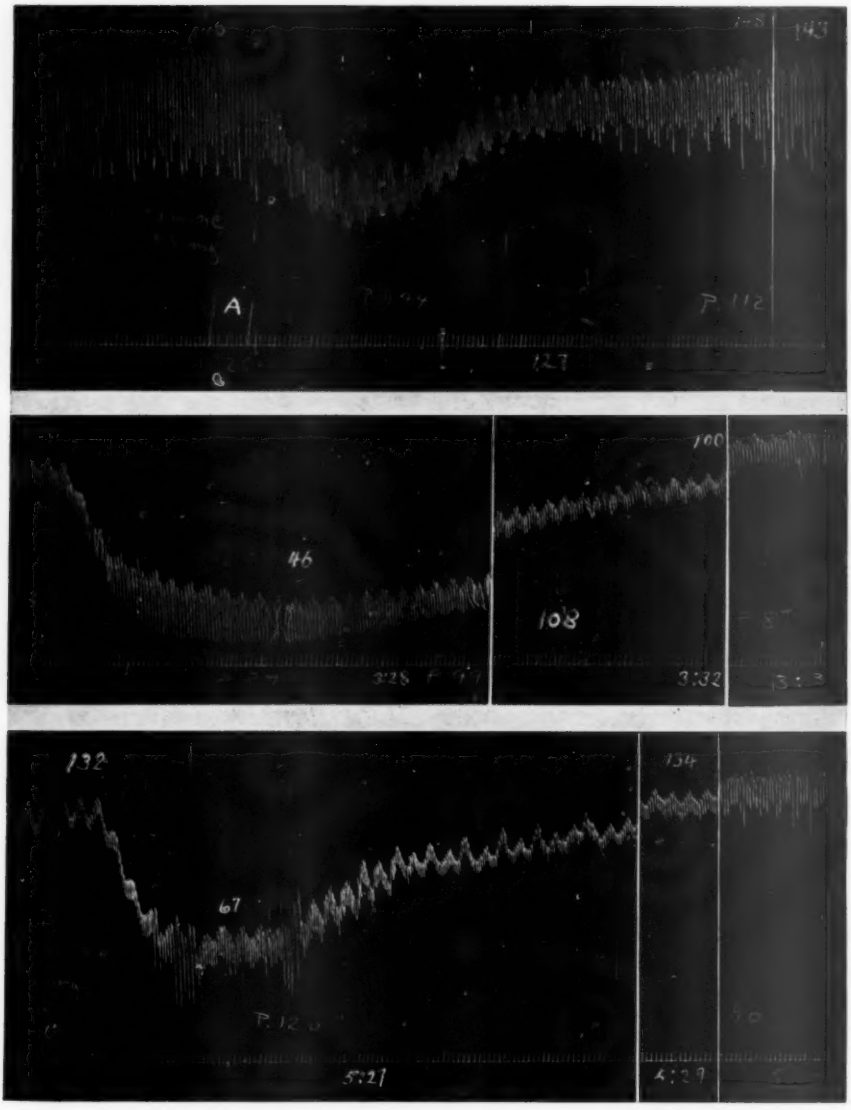

FIG. 6. Effect of histamine.

1:26 strip. Initial blood pressure 148 mm., pulse rate 84. The injection of .33 mg. of histamine intravenously at "*A*" caused a prompt fall of blood pressure to 88 mm., with a recovery in less than 1 minute to a stable blood pressure, reaching the original level in 1½ minutes.

3:28, 3:32, and 3:33 strips. TSB was induced 1½ hours after the first injection of histamine. At 3:27 (*B*) two hours after the first injection of histamine, the same dose of histamine

E. Histamine.—The effect of histamine intravenously in the TSB animal is seen in Fig. 6. Here, .33 mgm. of histamine in an 18 kilogram animal caused the blood pressure to fall from 148 mm. to 88 mm., a drop of 40.5 per cent., the downward trend was promptly arrested and it took 1½ minutes for the blood pressure to return to the pre-injection level. When the animal was under TSB, however, the same dose of histamine caused a fall of from 100 mm. to 46 mm., a fall of 54 per cent., the trough of the fall lasting much longer, and it took the blood pressure 5 minutes to return to its pre-injection level. When the recovery of the animal from TSB reached the point where the blood pressure had returned to the initial level, the same dose of histamine caused a fall from 132 mm. to 67 mm., a fall of 48 per cent., taking some 3 minutes to reach the pre-injection level. The doses of histamine were spaced exactly 2 hours apart in order to cancel out the possible factor of cumulative effect of previous doses of histamine.

FIG. 7. Effect of carbon dioxide.

Dog 18 kg. prepared as in previous experiments, with TSB induced at 1:05. The systolic blood pressure is 120 mm. Between 1:21 and 1:22 the animal was given 25 per cent. of CO_2 by inhalation. Note the prompt fall of blood pressure to 40, and that there were convulsions of muscles of the head. Note also the rise of blood pressure to original level two minutes after discontinuation of CO_2.

F. Carbon Dioxide.—Heymans has shown that in spinally anesthetized animals, the accumulation of CO_2 in the blood, instead of having a pressor effect as in the normal animal, has a depressor effect (7). This observation has been confirmed. Figure 7 shows the effect of the administration of CO_2 in the TSB animal. It will be seen that the blood pressure began to fall a few seconds after the administration, and kept falling until the gas was discontinued, when the blood pressure began promptly to rise, reaching its normal level in a minute or so. The con-

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was injected intravenously. Note the fall of systolic blood pressure to 46, the prolonged recovery taking about 5 minutes to reach the initial blood pressure at 3:32.

5:26, 5:29 and 5:30 strips. Partial recovery from TSB. The blood pressure is now 132. At 5:26, two hours after the second dose of histamine the third dose was given. Note the fall of blood pressure to 67 (a fall of 50 per cent.), the somewhat delayed recovery which is still prompter than that after injection "*B.*"

vulsive twitchings of the muscles of the head after the gas had reached a certain concentration in the blood is also an interesting feature.

SUMMARY AND COMMENT

When all the spinal nerves of an animal are paralyzed by a local anesthetic drug, the animal is said to be in a state of TSB. The picture presented by these animals may be taken as an end-point picture of the worst possible condition which can be caused by spinal anesthesia.

In the state of TSB in the lateral decubitus respiration is paralyzed, the tendon reflexes are absent, and the blood pressure is from 50 to 75 per cent. of the initial level. The pulse rate usually undergoes a four-way change: While the drug is taking effect, there is an acceleration, which is perhaps compensatory in character. At the full establishment of TSB, there is marked bradycardia, perhaps due to paralysis of the cardiac accelerators. During the recovery process, there is at first acceleration, followed by a return to normal as recovery becomes complete.

Under TSB, the animal's circulatory system is susceptible to a number of stresses. (1) The blood pressure level falls markedly when the animal is in the dorsal decubitus. The cause of this positional hypotension has not been elucidated but is perhaps associated with paralysis of the cardiac accelerator nerves. (2) The blood pressure falls slightly when the head of the animal is lowered (Trendelenburg position), and somewhat more when the head of the animal is raised (reversed Trendelenburg). (3) The homeostatic response to hemorrhage is so impaired that a small amount of bleeding which is easily tolerated by the normal animal brings about a shock level of blood pressure from which there is no recovery until the animal has recovered from TSB. (4) Administration of CO_2 causes a fall of blood pressure instead of a rise, as in the normal animal.

Recovery from TSB takes place in from 1 to 2 hours. The onset of the recovery is signaled by an acceleration of the pulse rate. The process of recovery takes place over an hour. Even when the tendon reflexes, the respiration and the initial blood pressure are restored, the homeostatic response to hemorrhage may still be impaired.

At this point, it will be interesting to compare the findings on TSB with our previous experimental spinal anesthesia studies. In these studies the fall of blood pressure to shock level was a fairly consistent finding. In view of the fact that in these experiments the animals were all on their backs, the low blood pressure was perhaps due to the combined factors of vasodilation and the dorsal decubitus. The phenomenon of hypotension as a result of CO_2 accumulation is also confirmed.

It would appear from the present studies that the motor effects of drugs used for spinal anesthesia deserve fully as careful consideration

as the sensory effects, and that an ideal spinal anesthetic drug would be one which will be maximally effective on the sensory elements and minimally effective on the motor.

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The Anesthesiology Section of the California State Medical Association will hold their annual meeting at Del Monte, California some time early in May. The program to be presented will be announced at a later date in this Journal. Karolina B. Jump, M.D., Secretary, 95 S. El Camino Real, San Mateo, Calif.

COMING MEETINGS OF THE NEW ENGLAND SOCIETY OF ANESTHESIOLOGY

DOWLING AUDITORIUM, BOSTON CITY HOSPITAL, BOSTON, MASS.

November 12, 1940—8 P.M.

"The Mechanics of Gas Anesthesia."

By

Albert H. Miller, M.D., Providence, R. I.
(Informal dinner at Hotel Kenmore at 6:15 P.M.)

WHITE AUDITORIUM, MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASS.

December 10, 1940—8 P.M.

"Fractional Spinal Anesthesia."

By

Morris J. Nicholson, M.D., Lahey Clinic, Boston, Mass.
(Informal dinner at Hotel Kenmore at 6:15 P.M.)

RELAXATION: A MEDITATIVE ESSAY

N. A. Gillespie, D.M. (Oxford), D.A. (England)

Despite the peaceful significance of this word, probably no subject has ever given rise to more bitter controversy between surgeons and anesthetists. Since surgeons, in the main, know little of the detail of anesthesia and its stages, and since anesthetists rarely have much first-hand experience of operating conditions, and seem therefore unable to sympathize with the surgeon's difficulties, it seems worth while to analyze the factors which are summed up in the word "relaxation."

A surgeon performing an operation within the abdominal cavity seeks fulfilment of the following conditions as far as may be expedient: complete muscular flaccidity, complete peritoneal flaccidity, minimal respiratory movements, and contracted viscera which will fall idly back into the abdomen when the walls are lifted. There are certain objections to the production of this state of affairs from the viewpoint of the patient and that of the anesthetist. Such conditions may be provided comparatively easily for lower quadrant operations, with more difficulty for mid-abdominal sections, and with most difficulty for procedures involving structures in the epigastric region. In this essay I have chiefly in mind the upper abdominal procedures such as gastrectomy, cholecystectomy, and splenectomy.

It must be explained that my early training was obtained in a country where most surgeons demand a greater degree of flaccidity than is usually considered adequate in the United States; and in an institution noted for the technical dexterity of its surgeons. Once provided with the above conditions they usually performed cholecystectomy within thirty minutes and gastrectomy within sixty minutes. The expression "deep ether anesthesia" meant, to us, the very shallow, rapid, panting respiration, widely dilated pupils not reacting to light, and dry cornea, usually described by textbooks as the "stage of overdose"; and it is in this sense that the term is used in this essay.

Such utter flaccidity both of musculature and peritoneum can, in my view, only be procured safely and consistently with ether as the anesthetic agent; and this only at a depth of anesthesia approximating the middle of the fourth plane. At such a depth, respiratory movement is so much impaired that a considerable degree of oxygen want will be present unless an excess of oxygen is added to the inspired atmosphere, and, even if this be done, anoxia may occur in the cells of the central nervous system. Further, under these conditions a considerable accumulation of carbon dioxide must occur in the "dead space" of the lungs. This is the chief objection to the method. Nevertheless ether, administered by the "open" or "semi-open" technique on a gauze mask and

with an excess of oxygen, does very nearly approach the surgeon's ideal of operating conditions. The safety of this agent is proverbial, and it is capable of producing these conditions in every patient, given sufficient skill in its administration.

When ether is administered by the "semi-closed" technique following a nitrous oxide induction, full muscular and peritoneal relaxation are easily attained. It is usually more difficult, however, to produce the same depth of anesthesia as by "semi-open" methods, and therefore, the respiratory movements are greater in volume. For reasons presently to be discussed, the hollow viscera tend to be distended when any of the gaseous agents are in use, and this is the chief disadvantage of the method.

Of chloroform I personally have no experience in this type of work, but I gather from those who have used it extensively that it will produce, in the lower second plane, conditions comparable to those seen with ether in the lower fourth plane, with the difference that respiration is much quieter. It is for these reasons that our forbears regarded its use as indicated for abdominal procedures. The regulations of one ancient teaching hospital in England require that when chloroform is used the indication for its use must be stated. In the anesthetic record books, which merely state that a certain agent was administered to a certain patient, on a certain day, for a certain operation, I have often seen: "Anesthetic: Chloroform. Reason: Abdominal Operation." In this particular institution this was the rule in the early years of this century, and the custom was not forsaken until "open ether" became popular in about 1910.

Cyclopropane is a baffling agent to evaluate from the standpoint of relaxation. It is probably the most difficult inhalation agent to administer with success. While in many ways it resembles chloroform, it differs markedly from it in the degree of flaccidity produced at a given plane of anesthesia in the muscles of the abdominal wall. With cyclopropane, as with ether, if reflex muscular spasm is to be avoided on surgical stimulus, the patient must be deeply anesthetized. Cyclopropane is not a respiratory stimulant in light anesthesia and therefore there is a tendency for the respiration to fail before sufficient depth is achieved to produce relaxation. This difficulty can only be overcome by the use of artificial means to maintain respiratory movement when spontaneous respiration has failed. But even when this is done, and deep anesthesia is achieved, the operating conditions are lacking in some respects. With cyclopropane, *muscular* flaccidity is rarely the equal of that seen with ether, although the peritoneal relaxation may at times exceed it. It appears to be a characteristic of the agent in that it often produces a state of affairs in which a comparatively rigid set of muscles overlies a surprisingly slack peritoneum. If, in an endeavor to secure complete flaccidity of all the structures comprising the abdominal wall the concentration of cyclopropane is increased, arrhyth-

mia is often encountered. In the present state of our knowledge it is not possible to evaluate the exact importance of this phenomenon, which often follows oxygen want consequent upon either depression of minute-volume or reflex closure of the glottis. Until further work elucidates the exact significance of these disorders of rate and rhythm, only the most experienced workers can afford to disregard them. They are much more frequently seen with cyclopropane than with ether. In the deeply etherized patient the abdominal wall can be picked up and held some three inches clear of the abdominal contents, which fall back, contracted, into the cavity. This state of affairs is rarely seen with cyclopropane for, however relaxed the patient, the loops of intestine are always comparatively large, and protrude through the peritoneum when it is opened. Surgeons accustomed to the operating conditions under deep ether anesthesia immediately protest at this point that "the guts are bulging out." It has been shown that the gaseous anesthetics are excreted, in small but definite quantities, into the lumen of the gut; and it may be presumed that herein lies the explanation of this phenomenon, which is equally marked when mixtures of nitrous oxide and ether are in use. On the other hand, it is probably true that the respiratory movements, which can be a source of annoyance to the surgeon, are more easily subdued when cyclopropane is in use. Deep ether anesthesia involves rapid panting respirations which can be very irritating, and these at best can only be minimized by keeping the plane of anesthesia so deep as to reduce the movement to an absolute minimum, unless some form of physiological apnea is produced.

Another possibility is the "high spinal." To be effective for operations above the umbilicus the subdural block must reach as high as the fourth dorsal segment. Even when this height is achieved the analgesia still does not affect the autonomic innervation of the upper part of the alimentary tract, and supplementary infiltration is usually necessary. Such a high spinal block involves a great strain on the circulatory system of the patient, and probably a longer period of paralysis of the intercostal muscles than results from the administration of an inhalation anesthetic. Even though the analgesia is perfect, most patients find it a severe emotional strain to remain conscious during operation, and suffer considerable discomfort from the abdominal manipulation involved. The surgeons I have above referred to, who had been used to working all their lives with patients deeply anesthetized with ether, were usually disappointed with the relaxation of muscles provided by spinal analgesia, for there is a definite difference between the muscular quiescence which obtains during spinal analgesia and the complete flaccidity or atonia seen when the tissues are saturated by ether.

The technique of administration of the anesthetic plays an important role in determining the extent to which ideal operating conditions can be produced, whatever the agent. Either oxygen want or carbon dioxide in excess can cause an artificial muscular rigidity. Any interfer-

ence with the patency of the patient's airway is the most usual way in which these conditions occur. Transitory obstruction is commonly seen in the edentulous patient whose tongue tends to become wedged between the lips during the movements of the second stage. Prophylaxis is always better than treatment; and this state of affairs can usually be avoided by placing a circular dental prop between the gums before beginning the induction. Obstruction above the level of the glottis is easily remedied in the third stage of anesthesia by means of an artificial pharyngeal airway.

Obstruction occasioned by the closure of the glottic opening, however, is a very different matter. Laryngeal spasm is often initiated by the presence of mucus in the pharynx which irritates the cords in light anesthesia. This can usually be prevented by suitable preanesthetic medication, and above all, by smooth induction. The latter will also obviate the variety of spasm which occurs as the result of the exhibition of too concentrated an anesthetic vapor, and is merely due to faulty technique. But reflex glottic spasm is most frequently occasioned by surgical stimuli in the abdomen, and results in a tightening up of all the structures, accompanied by an increase in respiratory effort. This situation constitutes a grave potential danger because it causes a complete respiratory obstruction which is extremely difficult to treat though easy to prevent; and it should not be permitted to occur. There are three methods by which laryngospasm may be prevented or treated. The first is anesthesia of such a depth as to abolish the reflex, which is one of the last to disappear. The second is local analgesia of the glottis by topical application. The third is endotracheal intubation. When spasm has once set in it is difficult to deepen the anesthetic because of the restriction of the airway. Deep anesthesia is therefore a successful prophylaxis, but a poor method of treatment. Local analgesia is satisfactory if efficiently applied through a laryngoscope; but I doubt the wisdom of paralyzing the cough reflex for some time to come in a patient who has had an upper abdominal intervention. I am firmly convinced that endotracheal intubation is the ideal prophylaxis against glottic spasm and I feel that its true place is as a preventative rather than as a palliative treatment after the damage has been done. Glottic spasm is unpredictable in its behavior and dangerous inasmuch as the anesthetist cannot control it; and therefore it should be made impossible as early in the course of the anesthesia as is practicable.

It is difficult to understand why "relaxation," judged by the criteria above enumerated, should always appear more satisfactory in a patient whose glottis has been intubated. Experience has convinced me that such is the case; to such an extent, in fact, that for years I have taught that complete relaxation of the abdomen cannot, except in the easiest cases, be obtained with any of the gaseous agents or nitrous oxide-ether mixtures, unless the patient is intubated. Perhaps it is because intubation makes for free breathing and so prevents the commonest cause of

oxygen want and an excess of carbon dioxide. Or perhaps it is that when the larynx cannot be closed the patient is unable to raise his intra-abdominal pressure by straining. Whatever the reason, I stand convinced that intubation is a sine qua non of efficient relaxation in the abdomen.

When the carbon dioxide absorption technique is in use, "quiescent" muscles (as opposed to "atonic" or "completely flaccid" muscles) are found in comparatively lighter anesthesia. On the other hand, the production of very deep anesthesia is a much slower and more difficult proceeding under these conditions. When once deep anesthesia has been reached, however, the absorption technique makes it possible to modify respiratory inconvenience to the surgeon by means of "controlled respiration." There is only one other way of doing this, and that is by exploiting the now almost obsolete technique of Meltzer and Auer and producing an acarbic apnea by the forcible insufflation of anesthetic gases. This achieves the same object by a totally different method. If, as it would seem, apnea, or something very close to it, materially facilitates the surgeon's work, then probably either technique is justifiable in these cases.

Quite apart from the operating conditions stands the fact that alone by one of these methods can carbon dioxide tensions be kept within normal bounds during very deep anesthesia, and controlled respiration would seem the more rational way of doing this. It still seems a moot point whether or not overdosage to the point of circulatory failure is a danger in practice if either of these techniques is used in very deep anesthesia. When a patient is in apnea it becomes very difficult to be certain of the plane of anesthesia. Since operating conditions are virtually identical in the third and fourth planes when a physiological apnea has been produced, there is the less need to risk disaster, and the patient can be spared unnecessarily deep anesthesia.

It is true that the exhibition of basal narcosis in some form can help in overcoming these difficulties. The various agents used for this purpose promote relaxation but also reduce respiratory volume. The latter attribute is a double-edged weapon because depression of respiration may in turn mean the inability of the anesthetist to cause sufficient of the inhalation agent to reach the alveoli and the blood to produce the deep anesthesia at which he aims.

Finally, some mention must be made of the respiratory complications which are among the most serious of upper abdominal surgery and which are responsible for a large proportion of postoperative deaths. The incidence of these appears to depend rather on the nature of the operation and the condition of the patient than on the anesthetic agent used. It has, however, been shown that their incidence is increased by the exhibition of basal narcosis. Many authorities have attributed them to the direct effects of the inhaled anesthetic vapors, and have advanced the view as an argument in favor of non-inhalation anesthesia in these

cases. My own experience, which is shared by better authorities, of using non-inhalation methods in the hope of minimizing respiratory complications has been uniformly disappointing. The use of any drug which produces respiratory depression is conducive to respiratory complications in the postoperative period, and this fact should, I believe, always be borne in mind. It is, however, my belief that the comfort of the patient deserves more consideration than it has heretofore been accorded. Most British anesthetists are agreed that the administration of ether in any form to a patient still conscious is so unpleasant as to be unjustifiable, especially since the great variety of alternatives available nowaways renders such techniques superfluous. In the main, patients seem to react towards the induction of anesthesia much as they do towards alcoholic excess: to the majority it is stimulating and not unduly unpleasant; to the minority it is an unpleasant ordeal under the best auspices and all but intolerable under others. A due sense of proportion should, I believe, be exercised, and the unfortunate minority should not be deprived of the consolation of a pleasant induction merely through fear of possible complications. Avertin and the barbiturates are most useful additions to our professional armamentarium yet I doubt the wisdom of using them consistently in upper abdominal cases.

These technical considerations, however, are only the dry bones of the subject of this essay. Both surgeons and anesthetists should have at least these objects in common: a real desire so to master the facts of their respective subjects that, by due co-operation and a sympathetic understanding of the problems of major abdominal surgery, they may eventually evolve methods known to produce the best results for the patient. It seems fundamental to me that the object of anesthesia is to enable surgical operations to be performed; and in the best interests of the patient the competence of the operation should be of the highest possible order. This is particularly true of abdominal surgery, where an operation of lesser skill may condemn the patient to much discomfort or disability. Abdominal surgery is a difficult and exacting pursuit in which results seem to turn largely on gentleness. It seems to be beyond argument that the more nearly are these conditions of absolute relaxation approached, the more atraumatic is the operative procedure likely to be. It is the common experience of anesthetists that the degree of postoperative upset in the patient is profoundly modified by the amount of handling of the viscera, the quantity of packing that has been used, and the amount of trauma to the recti and diaphragm from forcible retraction. Effective relaxation reduces these to a minimum—at the price of really deep anesthesia. This probably does the healthy patient little harm if it is not maintained for excessive lengths of time, and it is less damaging than the surgical trauma to which light anesthesia usually gives rise. If this be true, then it follows that the surgeon must choose between two alternatives: either he must learn to exploit ideal conditions to enable his work to be quickly and easily done,

or he must work deliberately at a much lighter plane of anesthesia and tolerate its disadvantages.

It is true both of surgeons and anesthetists that they chiefly "learn by trying." If an anesthetist does not from time to time experiment with new agents and methods he will cease to keep abreast of the advances of his subject. When he thus experiments he is unlikely to produce as efficient relaxation as he obtains by methods with which he is familiar. Since in the past the anesthetist has usually been dominated by his surgeon, he has found it expedient to do his very best and to risk no experiments when the surgeon himself is operating. The experimentation has usually been deferred until one of the surgeon's juniors—Residents, First Assistants, House Surgeons, or Interns—has been allowed to "finish the list." This means in practice that the unfortunate patient is not only subjected to the risks attendant upon inexperienced surgery, but also to the double risk of surgery under very difficult conditions. In our profession, as in most, there can be no argument with one's seniors; and since the anesthetist is usually senior to the younger surgeons, the latter are forced to learn under the most trying conditions. This is surely entirely wrong, both to the patient and to the surgeon. A man of many years' experience should be able to work under certain mechanical difficulties; but when a young man is just beginning to operate, an already difficult task should be made as easy as possible, both for the patient's sake, and for the surgeon's. Conversely, the experienced senior surgeon should be willing, from time to time, and provided he is aware of what is being done, to work under somewhat imperfect conditions in order that knowledge may advance.

If the recent events in the world of politics have any meaning, they should teach us afresh the truth of the saying that "two blacks don't make a white." This is equally true of surgery and anesthesia. For generations anesthetists have had to tolerate, for economic reasons, dogmatic interference from surgeons in their own province: only in recent years are surgeons coming to regard their anesthetist as a colleague and advisor. Surely our attitude should rather be: "tell me what conditions you need in order to do your work most effectively, and I will do my best to supply them"; and his reply should be to outline these conditions and to add "it is for you to decide how these things should be realized." Whenever an individual case presents unusual difficulties this should be the attitude of mind in which it should be approached by both parties.

Unpleasant operating conditions are often not apparent on inspection from the angle of view available to the anesthetist, and conversely a surgeon completely absorbed in a difficult operation may perhaps be forgiven if, in the heat of the moment, he is apt to attribute his mechanical difficulties to the shortcomings of his anesthetist. Mistakes will often be made in perfectly good faith by both parties; but they should be sufficiently honest to admit to those mistakes later, for strict

honesty is indeed the best policy in this issue. "Tout comprendre c'est tout pardonner," and for that reason it is essential that a surgeon should have had some first-hand experience in the administration of anesthetics, and that an anesthetist should have learnt by bitter experience what it means to wrestle with unrelaxed abdominal muscles.

Although it is scarcely a technical consideration, personal friendship between surgeon and anesthetist is probably the greatest help in realizing these ideals. Men only speak freely and honestly with those whom they like. When such an understanding becomes the rule then the word "relaxation" will cease to represent, surgically, a travesty of its true meaning.

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The Library and Museum of the American Society of Anesthetists is open daily from 9:00 A.M. to 5:00 P.M., Mondays through Fridays (holidays excepted), in Room 1503, 745 Fifth Avenue, New York City. For special appointments at other times, call Susquehanna 7–5411. It was established a few years ago for the benefit of all in the medical professions. It is also open to the lay public, but is especially for the use of physicians interested in anesthesia. Admission is free. Guests are requested to register.

There are many interesting items in the library collection of the American Society of Anesthetists which can be obtained for local exhibits by making arrangements with the Librarian. One such rare item is a copy of John Snow's first edition on "Ether." This copy was Snow's personal desk copy and was never bound. There are more than 500 items in the library including all the recent books and journals on anesthesia. The books cannot be borrowed except by members of the Socety, but transcripts, photostats, and microfilm copies of certain rare books and articles may be obtained for personal use by writing to the Librarian. Books may also be obtained for scientific exhibits if the proper requirements are met.

The museum of the American Society of Anesthetists now occupies 5 large cases and 24 smaller cases. The accessions date from the beginning of modern anesthesia to the present time. Among the collection may be seen the original Boothby-Cotton gas ether machine, the first gas machine on the West Coast of the United States, an early American chloroform mask, a Morton inhaler, the first Furniss inhaler, the first cyclopropane gauge, the first American Avertin kit, and numerous other originals. For the February meeting of the American Society of Anesthetists the Library and Museum Committee expect to have ready a special display showing the development of the anesthetic mask. All anesthetists are urged to enlarge this growing collection by sending any material they may have to the Library-Museum Committee. If you are holding a special meeting on anesthesia at which exhibits are desired, assistance in preparing them may be obtained by writing to the Chairman of the Museum Committee.

THE CONTROL OF GASTRO-INTESTINAL TONE AND MOTILITY WITH NOVATROPINE *

STEVENS J. MARTIN, M.D., AND ROBERT C. BATTERMAN, M.D.

SURGICAL manipulations involving the gastro-intestinal tract are more conveniently accomplished and the results more satisfactory if the anesthetist has complete control over the contents of the abdomen as well as its muscular walls. The better application of regional anesthetic technics, the introduction of new drugs, the use of endotracheal airways and controlled respirations have provided safe means for controlling abdominal muscles. Spinal anesthesia and various drugs have made it possible to constrict the intestines during surgery and thereby facilitate exposure of abdominal contents. It has been observed, however, that increasing intestinal muscular tone may not always add to the convenience of operative procedures. The difficulties of placing sutures are often increased with the intestinal lumen practically eliminated and the musculature strongly contracted. Moreover, some dangers have been recognized associated with increasing tone of the intestines. Rupture of the obstructed gut has been reported following spinal anesthesia (1). Sutures placed in contracted intestines may not be hemostatic after the gut has regained normal tone, and more particularly is this true if they are placed when the arterial tension is low and bleeding points are not easily recognized, as often prevails during spinal anesthesia.

It has been observed clinically and determined experimentally that Novatropine † may be employed in amounts that can be used with safety to eliminate motility and decrease muscle tone of the intestines (2). This report includes these observations on unanesthetized and anesthetized humans.

UNANESTHETIZED PATIENTS

A series of experiments was completed to study the effects of Novatropine on various portions of the gastro-intestinal tract of unanesthetized human subjects. The method for study utilized direct intubation of the gastro-intestinal tract with inflatable balloons. Although the technics employed do not satisfy all the requirements necessary for a complete analysis of gastro-intestinal motility, they nevertheless furnish sufficient and satisfactory gross evidence of the inhibitory effects of antispasmodic drugs.

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† Novatropine is the trade name for homatropinemethyl bromide. The drug was supplied through the courtesy of the Campbell Products Co. in convenient ampoules with 1 cc. aqueous solution containing 5 mgm. Novatropine.

The Miller-Abbott tube with double lumen and attached balloon was used for studies on the stomach and ileum. Passage into the latter was greatly facilitated and was confirmed throughout the period of study by repeated fluoroscopic examinations. Observations on the colon were completed with subjects having functioning permanent

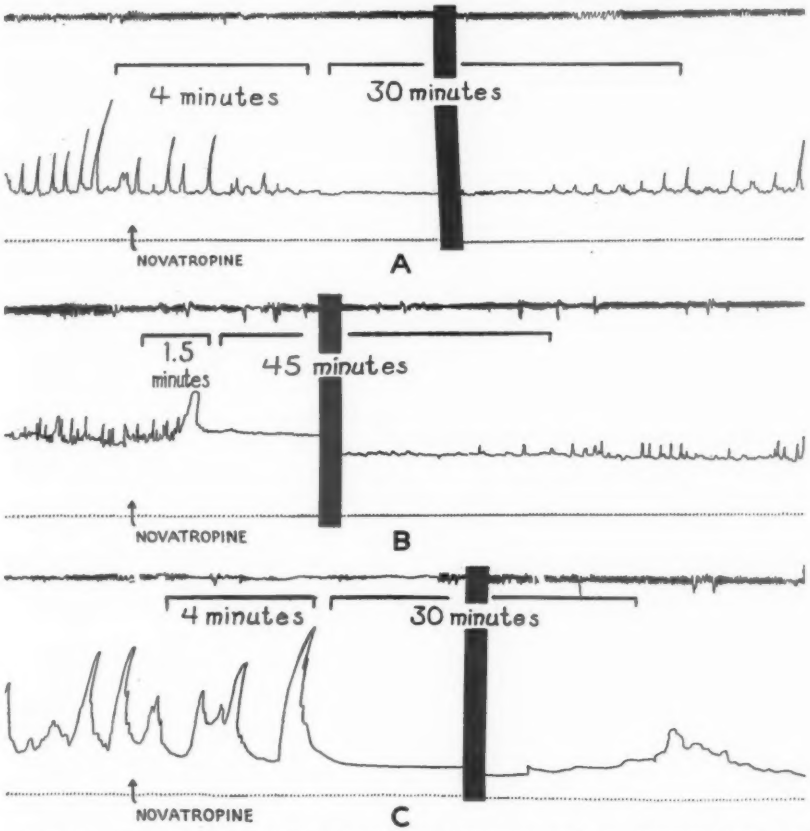

FIG. 1. Effect of Novatropine administered intramuscularly on stomach, ileum, and colon. *A*—Action of 5.0 mgm. of Novatropine on gastric motility. *B*—Action of 2.5 mgm. of Novatropine on the motility of the small intestine. *C*—Action of 5.0 mgm. of Novatropine on colonic motility.

colostomies. A balloon attached to a Levine tube was inserted by gentle manipulation into the lumen of the proximal colostomy opening for a distance of 15 to 30 centimeters and maintained in place by adhesive strapping. All subjects were studied under basal conditions. Thus, the disturbing effects of food, tobacco or other medications were eliminated and interference with any possible effect of novatropine avoided. In addition, those subjects with a colostomy had a cleansing enema at least two hours before insertion of the balloon.

The tracing, recorded on a kymograph, was taken with the subject in the supine position. A preliminary control tracing of 30 to 60 minutes' duration was taken in each instance. This time was sufficient to allow the particular portion of the gut under observation to adjust itself to the pressure and presence of the balloon. After a satisfactory control tracing, novatropine was administered intramuscularly in doses of 2.5 to 5.0 mgm. An exception was made in one subject who received 1.25 mgm. A continuous tracing was thereafter taken until either the activity of the gut had returned to normal or the subject became uncooperative because of the duration of the experiment. Specimen tracings are shown in Fig. 1.

TABLE 1

EFFECT OF NOVATROPINE ADMINISTERED INTRAMUSCULARLY ON THE STOMACH, ILEUM AND COLON

Site of Balloon	Dose in Mgms.	Onset of Effect Minutes	Effect	Duration Effect Minutes	Remarks
Stomach.....	2.5	7	Complete cessation of motility	30	Return of normal activity—1 hour.
Stomach.....	2.5	6	Complete cessation of motility	60	
Stomach.....	2.5	7	Complete cessation of motility	18	Return of normal activity—33 minutes.
Stomach.....	5.0	2½	Complete cessation of motility	60+	
Stomach.....	5.0	1	Complete cessation of motility	45	
Stomach.....	5.0 5.0	5 5	Complete cessation of motility Complete cessation of motility	55 65	Decreased activity for 90 minutes.
Stomach.....	5.0	4	Complete cessation of motility	30	Return of normal activity—1 hour.
Stomach.....	5.0	6	Complete cessation of motility	90	
Ileum.....	1.25	10	Complete cessation of motility Reduction of tone	15 30	Return of normal activity—30 minutes.
Ileum.....	2.5	1½	Complete cessation of motility Reduction of tone	45	Return of normal activity—1 hour.
Ileum.....	2.5	5	Complete cessation of motility Reduction of tone	5	Decreased activity for 60 minutes +.
Colon.....	2.5	4½	Complete cessation of motility	35	Return of normal activity—45 minutes.
	2.5	4	Complete cessation of motility Reduction of tone	45	Decreased activity for 90 minutes +.
	5.0	4	Complete cessation of motility	30	Occasional activity but no return to normal for 60 minutes +.
Colon.....	2.5	5	Complete cessation of motility	60+	
	5.0	1½	Complete cessation of motility Reduction of tone	90+	
	5.0	3	Complete cessation of motility Reduction of tone	60	
Colon.....	2.5	3	Complete cessation of motility	45	Decreased activity for 90 minutes +.
Colon.....	2.5	4	Complete cessation of motility	40	Decreased activity for 70 minutes +.

The results are summarized in Table 1. In each instance, regardless of the portion of gut under observation, there resulted a complete cessation of motility, the onset and duration of which depended upon the dose of novatropine administered. With 2.5 mgm., the effect on the stomach was gradual in onset, reaching its peak within 6 to 7 minutes.

In the case of the ileum and colon, the effect with this dose appeared to be slightly more rapid, usually occurring within 5 minutes. With 5.0 mgm., the effect on the stomach and colon occurred on the average within 4 minutes. The gut remained completely quiescent for 5 to 60 minutes with 2.5 mgm. and from 30 to 90 minutes with 5.0 mgm. Although gradual recovery occurred from then on, in many instances complete return to normal was not recorded during the time limits of the experiment. In addition to complete cessation of motor activity of the ileum and colon, these particular portions of the gastro-intestinal tract showed a marked reduction of tone.

A series of control cases using atropine in therapeutic doses was completed to demonstrate the ineffective action of this drug upon motility of the gastro-intestinal tract as compared with novatropine. These results will be contained in a more complete pharmacological study of novatropine now in preparation.

ANESTHETIZED PATIENTS

Another series of observations was completed during anesthesia for operations upon the gastro-intestinal tract. The subjects selected were the consecutive cases from a general surgical service. No consideration was given to age, sex, physical condition or nature of the operation. Novatropine was given subcutaneously as preanesthetic medication with morphine. The amount of morphine varied with the indications for this drug from 8 to 16 mgm. (⅛–¼ gr.). The effect of novatropine was not obviously influenced by these amounts of morphine. Novatropine was given in doses of 1.25 mgm. and multiples of this amount to 7.5 mgm. Preanesthetic medication was administered from 60 to 90 minutes prior to induction of anesthesia. Ether and cyclopropane were the inhalation anesthetic agents administered by the carbon dioxide absorption technic.

The results obtained are shown in Table 2. With the 1.25 mgm. dose, the decrease in tonus of the gastro-intestinal tract was not marked. Twice this amount was regularly effective in decreasing the tone, and the 5 mgm. dose entirely eliminated tonus except in two of the ten cases given cyclopropane. When 7.5 mgm. were given, tonicity was always eliminated. Motility was not present in any patient having received 1.25 mgm.

It was further observed that effects other than those on the gastro-intestinal tract were no different with novatropine than are anticipated by previous experience from atropine in 0.6 mgm. (1/100 gr.) doses. Mouth dryness, depression of mucous secretions, and vagal effects upon the heart rate are essentially the same from the two drugs with the amounts used. No untoward postoperative reactions were noted that could be attributed to novatropine in this series of cases.

The maximum effects from novatropine are never delayed beyond one hour, the earliest time when these observations were made. Labo-

TABLE 2

EFFECT OF NOVATROPINE ADMINISTERED SUBCUTANEOUSLY UPON THE TONICITY OF THE ABDOMINAL GASTRO-INTESTINAL TRACT

Novatropine Mgm.	Cases	Anesthetic Agent	Gastro-intestinal Tone *
1.25	6	Ether	1 to 2
	4	Cyclopropane	2
2.50	4	Ether	1 to 2
	4	Cyclopropane	1 to 2
3.75	6	Ether	0 to 1
	4	Cyclopropane	1
5.0	12	Ether	0
	10	Cyclopropane	0 to 1
	3	Spinal-procaine	3
7.5	5	Cyclopropane	0

* *Code:* 0—None 1—Slight 2—Normal 3—Increase.

ratory and other clinical evidence indicate that the drug is effective much sooner after parenteral injection.

Novatropine was given to three patients who were to receive spinal anesthesia. The effects upon the gastro-intestinal tract were not observed to differ from those regularly obtained with spinal anesthesia.

SUMMARY

Studies on unanesthetized and anesthetized humans revealed that a parenteral injection of novatropine in doses of 2.5 to 7.5 mgm. eliminates or markedly reduces the tone and motility of the gastro-intestinal tract. Novatropine may thus be used to advantage for this purpose during abdominal surgery.

These studies were completed under the direction of Professors Arthur C. DeGraff and E. A. Rovenstine, Departments of Therapeutics and Anesthesia respectively, New York University College of Medicine, New York City.

477 First Ave.

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THE ANESTHETIC POTENCY OF SOME NEW PIPERIDINE DERIVATIVES *

WILLIAM H. HUNT AND RUSSEL J. FOSBINDER

INTRODUCTION

THE pharmacology and toxicity of a new series of substituted benzoic esters, derived from 2-piperidine ethanol (1), have been investigated with the object of evaluating their relative merit as local anesthetics. The anesthetic potency of these compounds was investigated for (*a*) surface anesthesia, (*b*) infiltration anesthesia, (*c*) intradermal anesthesia, (*d*) intraspinal anesthesia, and (*e*) sciatic nerve block. A study was made of the effects produced upon blood pressure and respiration of the anesthetized cat, when the compounds were administered intravenously in sub-lethal doses. The toxicity was determined by (*a*) subcutaneous injection in the mouse, guinea pig, and male white New Zealand rabbit; and (*b*) intraspinal and intravenous injection in the rabbit. Cocaine HCl, procaine HCl, and metycaine † were used for purposes of comparison. The identification numbers, chemical names and structural formulas of the compounds studied are listed in Table 1.

SURFACE ANESTHESIA

The cornea of the rabbit eye was used to determine the topical anesthetic activity. Each determination was made upon a different animal and at no time was there an interchange of compounds upon the same animal. Two per cent. solutions of many of the clinically useful local anesthetics are generally recommended for topical application to mucous surfaces. For the purpose of comparing the topical anesthetic activity of the series, we studied the duration of corneal anesthesia produced by solutions of this strength.

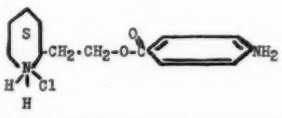
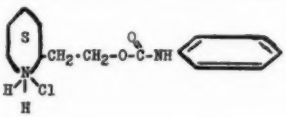
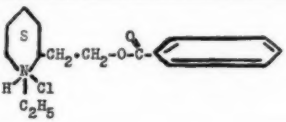
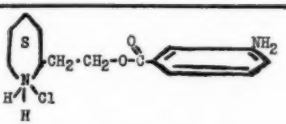
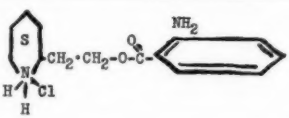
One-tenth cc. of a 2 per cent. solution of the anesthetic was instilled into the eye by holding the lower lid away from the cornea. After instillation, the lid was slowly returned until the fluid covered the lower three-fourths of the cornea. One minute later the lid was allowed to resume its normal position. The onset and duration of anesthesia was then determined by applying the blunt end of a uniform bristle to the anesthetized portion at an arbitrarily established rate of 100 times per minute, observing the abolition and reappearance of the wink reflex.

Cocaine HCl and metycaine were employed as control agents. The test for each new agent was carried out on one eye, while the control test was determined simultaneously on the other.

* From the Research Laboratories, The Maltbie Chemical Company, Newark, New Jersey.
† Generously supplied by Eli Lilly and Company.

The duration of corneal anesthesia produced by 2 per cent. solutions of the compounds revealed that PT–19 acted approximately twice as long as cocaine HCl and approximately eight times as long as metycaine. The average durations of anesthesia for the series were found

TABLE 1

Identification Number	Name of Compound	Structural Formula
PT-1	Beta-2-piperidyl-ethylparaaminobenzoate Hydrochloride	
PT-4	Beta-2-piperidyl-ethylphenylurethane Hydrochloride	
PT-6	Beta-2-(N-ethyl-piperidyl) ethylbenzoate Hydrochloride	
PT-14	Beta-2-piperidyl-ethylmetaaminobenzoate Hydrochloride	
PT-19	Beta-2-piperidyl-ethylorthoaminobenzoate Hydrochloride	

to be: PT–19, 100 minutes; cocaine HCl, 56 minutes; PT–1, 47 minutes; PT–14, 27 minutes; PT–6, 22 minutes; metycaine, 13 minutes; PT–4, 9 minutes. PT–4 and 6 appeared to be slightly irritant to the cornea as evidenced by the reaction of the test animal.

The possibility of corneal damage following application of these compounds in various concentrations was investigated by the sodium fluoresceine technique (2) using a 2 per cent. solution of the dye as a diagnostic agent. In a concentration of 2 per cent. all of the compounds with the exception of cocaine HCl failed to produce any recognizable damage. At higher concentrations definite injury to the cornea was observed with all compounds, but PT–19 and PT–1 produced less damage than others of the series.

Considering the evidence, it is believed that PT–19 and PT–1 offer certain advantages for usage as corneal anesthetics, particularly the former when a more prolonged period of anesthesia is desired. From this evidence it is inferred that mucous membranes, such as that of the nose and throat, should also be readily anesthetized, though data on this use is not at present available.

INTRASPINAL ANESTHESIA

The duration of sensory anesthesia produced by subarachnoidal injection of local anesthetics in relation to their toxicity is, from the clinical standpoint, the determining and important factor in ascertaining the limits of a satisfactory sensory anesthesia.

Comparative data on the action of the new compounds as spinal anesthetics were obtained using the rabbit as the test animal. Although the lack of spinal fluid in the rabbit, in contrast to larger animals, offers a disadvantage for comparative study, Bieter, et al. (3), have concluded that it is much easier to study the exact pharmacological actions of given concentrations of local anesthetics when they are undiluted with spinal fluid.

Following, in general, the procedures described by Bieter et al. (3), a series of 468 rabbits was used for a determination of the minimal anesthetic dose, both sensory and motor, the maximal effective dose and the minimal lethal dose of five new compounds and two control agents. The M.A.D. was that dose which produced sensory anesthesia in six of eight animals, while the M.L.D. was that dose which produced immediate death in six of eight animals. The experimental results, in condensed form, are shown in Table 2.

TABLE 2

MINIMAL ANESTHETIC, MAXIMAL EFFECTIVE AND MINIMAL LETHAL DOSE OF LOCAL ANESTHETICS USED INTRASPINALLY

Compound	Strength of Solution	M.A.D.		Strength of Solution	M.L.D.		Strength of Solution M.E.D.	Duration of Anesthesia at M.E.D.	Therapeutic Ratio
		Spinal Length	Body Weight		Spinal Length	Body Weight			
	per cent.	mgm./cm.	mgm./kgm.	per cent.	mgm./cm.	mgm./kgm.	per cent.	ave. in min.	M.L.D. % / M.A.D. %
PT-1.....	0.35	0.064	0.8310	4.00	0.8000	10.920	2.00	62.80	11.4
PT-4.....	0.80	0.160	2.8605	7.53	1.5060	23.450	3.00	72.14	9.4
PT-6.....	0.80	0.160	2.6230	9.70	1.9400	29.980	1.50	20.80	12.1
PT-14....	0.50	0.100	1.3720	8.00	1.6000	24.620	4.00	59.85	16.0
PT-19....	0.30	0.060	0.8653	10.39	2.0780	29.970	2.50	95.25	34.6
Procaine HCl....	0.90	0.179	1.6850	7.00	1.4000	15.504	5.00	44.50	7.8
Metycaine	0.80	0.160	2.3700	8.00	1.6000	24.120	1.50	36.00	10.0

M.A.D.—Minimal Anesthetic Dose.
M.E.D.—Maximal Effective Dose.
M.L.D.—Minimal Lethal Dose.

If the therapeutic ratio, M.L.D. per cent./M.A.D. per cent. is acceptable as an index of safety, then it may be seen that the margin of safety for the series decreases in the following order: PT–19, 14, 6, 1, 4, metycaine and procaine HCl. The durations of sensory anesthesia produced by safe doses of PT–19, 14, 4 and 1 greatly exceed those induced by comparable doses of procaine HCl and metycaine, and in this respect the new compounds appear to offer a distinct advantage. Hence it is possible that PT–19, particularly, may be of unique value clinically owing to its safety as well as its long duration of action.

Rabbits receiving sub-lethal intraspinal doses of the anesthetics recovered from anesthesia without exhibiting permanent damage and in no instance was there evidence of injury of the cord structure. With lethal doses the majority of deaths were of an immediate nature, and it was assumed that death was caused by central respiratory depression, since definite and distinct heart beats could be detected for a short time following cessation of respiration.

In agreement with the observation of Bieter, et al. (3), on other local anesthetics, we have found that the new compounds, when injected intraspinally in the rabbit, exert a more powerful effect upon motor rather than on sensory nerves, in contrast to the opposite relationship shown to exist in spinal anesthesia in man.

Sciatic Nerve Block, Intradermal and Infiltration Anesthesia

In the evaluation of new local anesthetics much useful information may be obtained by the determination of duration of anesthesia produced by varying concentrations of solutions in inducing nerve-block, intradermal anesthesia, and particularly infiltration anesthesia. Nerve block and intradermal anesthesia may be conveniently studied by use of the techniques described by Shackell (4) and Shackell and Rose (5), in which the guinea pig is used as the test animal. The procedure developed by Tatum (6), in which the anesthetic solution is infiltrated into the subcutaneous tissue about the external canthus of the rabbit eye, was employed for the determination of the duration of infiltration anesthesia.

A summary of the data obtained by application of these methods to the new series of compounds is given in Table 3. Three hundred and fifteen guinea pigs and 400 rabbits were used in obtaining the complete results. In general, it may be noted that the duration of anesthesia produced by PT–1, 4, 14 and 19 compares favorably or is superior to that produced by procaine HCl and metycaine. With a concentration range of 0.25 to 2.0 per cent. none of the anesthetics employed produced obvious irritation or inflammation of the tissue at the site of injection. The minimal anesthetic concentrations, in the case of nerve block, were found to be lower for sensory than for motor fibers, in contrast to the results obtained by intraspinal injection in the rabbit.

TABLE 3

AVERAGE DURATION OF ANESTHESIA

Compound	Sciatic Nerve * Block Guinea Pig		Intradermal † Guinea Pig		Infiltration † Rabbit	
	Concentration					
	1.0 per cent.	2.0 per cent.	1.0 per cent.	2.0 per cent.	1.0 per cent.	2.0 per cent.
	min.	min.	min.	min.	min.	min.
PT-1	19.5	29.4	55.0	71.8	37.0	53.0
PT-4	5.7	13.3	47.4	63.6	31.0	47.0
PT-6	11.8	27.5	37.0	52.6	27.0	30.0
PT-14	12.6	14.7	44.6	56.2	37.0	53.5
PT-19	14.1	26.1	52.2	72.5	31.0	62.0
Procaine HCl	15.9	28.0	32.2	42.4	22.0	28.0
Metycaine	10.9	19.9	40.8	56.8	37.5	61.25
Cocaine HCl	19.9	52.5	34.2	LD 100	24.0	27.0

* 0.2 cc. of solution injected.
† 1 cc. of solution injected.

TOXICITY

A comparison of the toxicities of the piperidine derivatives and the control compounds, obtained by the subcutaneous and intravenous injection in several species, is given in Table 4.

TABLE 4

TOXICITY

Compound	Subcutaneous Rabbit		Intravenous Rabbit	Subcutaneous Guinea Pig	Subcutaneous Mice M.L.D.—100
	Single Injection	Multiple Injection Range of M.L.D. 2–10 Per Cent. Solutions			
	mgm./kgm.	mgm./kgm.	mgm./kgm.	mgm./kgm.	mgm./kgm.
PT-1	250.00	88.40–252.75	17.0	196.23	350.00
PT-4		125.51–252.75	20.0	456.32	650.00
PT-6		286.46–552.48	20.0	439.23	1700.00
PT-14	500.00	225.39–382.12	20.0	315.45	1250.00
PT-19	150.00	83.41–119.41	15.0	153.34	800.00
Procaine HCl	800.00 *	152.84–500.00	45.0	695.04	
Metycaine			17.0	267.59	1500.00
Cocaine HCl		78.43–195.31		64.12	300.00

* Taken from literature (7).

It is of considerable interest to compare the values for the M.L.D., obtained by infiltrating the abdominal area of the rabbit with a given volume of solution, using the single and multiple injection procedures. Referring to Table 4, it may be noted that the subcutaneous toxicity determined by the single injection technique is substantially lower than

that found for the same anesthetic by employing multiple injections of a dilute (2 per cent.) solution. Furthermore, concentration plays an important part, for on increasing the concentration to 10 per cent., in the case of multiple injections, the toxicity decreases stepwise and the limiting values approach those obtained by the single injection method. It is evident that the area infiltrated and the concentration of the anesthetic must be determining factors for the rate of absorption from the site of injection.

Since it is of considerable importance to know if the animal under the effects of a lethal dose of these compounds can be saved by the administration of a barbiturate, as in the case of procaine, the following type of experiment was carried out: An optimal dose of 25 mgm. per kgm. of nembutal * was administered intravenously, followed immediately by subcutaneous injections (multiple) of a lethal dose of the anesthetic. Thirty-one out of a series of 32 animals treated according to this technique survived fatal doses of the new compounds and the control anesthetics.

Following the single injection method, and administering Nembutal intravenously as required, it was found that rabbits failed to survive in the case of PT–1, when injected with a dose exceeding the M.L.D. Animals injected with two times the M.L.D. of PT–14 and two and one-half times the M.L.D. of PT–19 were saved by the barbiturate. These findings appear to be significant in that unavoidably dangerous doses of the anesthetics may be antidoted, thus increasing the potential margin of safety.

Effect on Blood Pressure and Respiration

A series of experiments was performed to determine the effect of these compounds upon the blood pressure and respiration of the cat, anesthetized by an intraperitoneal injection of an aqueous solution of urethane (1 gram per kgm. body weight).

All of the compounds and the control agents produced a definite fall in blood pressure following intravenous administration of 3, 4 and 8 mgm. per kgm. The order of activity in lowering of blood pressure by a dose of 4 mgm. per kgm. was found to be: metycaine > cocaine HCl > PT–1 > 6 > 19 > procaine HCl > PT–4 > 14. When a dose of 8 mgm. per kgm. was injected the order of activity was: PT–6 > metycaine > PT–19 > procaine HCl > PT–1 > 4 > 14.

In most cases the fall in pressure was transitory in nature, but in some instances the pressure failed to return to the level established prior to the administration of the anesthetic. Since the magnitude of the change was not influenced by the prior administration of atropine sulfate, it may be said that the fall in pressure was not due to parasympathetic stimulation.

* Generously supplied by Abbott Laboratories.

When the animal was perfused with a 2 per cent. solution of each compound until death occurred it was observed that a simultaneous stoppage of the heart and respiratory movements took place with the following: PT–14, 6, 14 and 19. Metycaine, PT–1 and procaine HCl produced cessation of respiratory movements approximately one to two minutes prior to heart stoppage, while cocaine HCl produced cessation of respiration just before heart stoppage was observed.

The selection of active anesthetics of the series for clinical study may be based on a consideration of the toxicity, manner of death, the ability of a barbiturate to reduce toxicity, the type and time of duration of anesthesia, the effect of sub-lethal doses upon the blood pressure and respiration, and the effect produced upon tissues, immediately upon injection and after the anesthetic action has disappeared. The anesthetic index is of some importance, but too much emphasis should not be placed upon these values except for comparative purposes.

PT–1, 14 and 19 appear to be worthy of clinical investigation, particularly for corneal, topical and spinal anesthesia.

CONCLUSIONS

1. On the basis of animal experimentation PT–19 appears to be superior to other local anesthetic agents for use on the cornea in that it has a longer period of action and a lessened likelihood of producing corneal damage.

2. For spinal anesthesia, PT–19, PT–1 and PT–14 appear to excel the other anesthetics to which they were compared, particularly from the point of view of duration of action and relative safety.

3. None of the series of new anesthetics appears to be equal to procaine in safety and efficiency for purposes of infiltration anesthesia.

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THE FATE OF ANESTHETIC DRUGS IN THE BODY *

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THE factors which influence the pharmacological response of an organism to a drug are its chemical nature, which determines the type of response and toxicity; its concentration; and its duration of contact with the cells. The last factor, with which this discussion is concerned, varies with the ease of elimination or conversion of the drug to an inert substance by a biochemical mechanism. The conversion of a physiologically active substance to one less active, or physiologically inert, has been called detoxification. The term is used occasionally in a pharmacological sense to describe the reversal of the activity of one drug by another, such as occurs when a narcotic effect is reversed by an analeptic. This, however, is merely the addition of a second drug which alters the action but does not influence the destruction of the first. The term detoxification is more properly used in a biochemical sense.

A variety of chemical reactions occur within the body to which a foreign reactive substance may be subjected. Four important general mechanisms will be considered. The first is oxidation, or the addition of oxygen. A compound may be partially oxidized and lose its identity, or completely burned with the liberation of energy, carbon dioxide, and water. Primary alcohols are destroyed in this manner. If not amenable to oxidation, the compound may be subjected to a second mechanism, reduction. Reduction, the converse of oxidation, is completed by the addition of hydrogen. Aldehydes may be converted to alcohols in this manner. If not oxidizable or reducible, the compound may be subjected to a third mechanism, hydrolysis. Hydrolysis occurs when the compound splits into products which utilize the hydrogen and hydroxyl of water. An example is the cleavage of acetyl salicylic acid to acetic and salicylic acids. If not susceptible to any of these three mechanisms, the compound may undergo a more important biochemical reaction known as conjugation. Conjugation entails the addition of a new radical to the molecule which changes the chemical nature and physiological activity. Since a variety of radicals may be involved in conjugation, this mechanism is considered under a number of subdivisions. The more prominent of these occurs when various acids, such as acetic, amino acetic, cysteine, or glycuronic, are involved. Glycuronic acid forms either glucosides from alcohols or esters from acids. This mechanism is important since a number of anesthetic drugs are detoxified in this manner. The methyl group may be added to such compounds

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as pyridine. (It may also be removed from such compounds as caffeine.) The methyl radical and others entering into conjugation are derived from endogenous sources within the body, and their production is not influenced by ingestion of products thought to be their sources.

The various reactions of detoxification may occur singly, in combination, or follow each other. A compound may be reduced, then conjugated and excreted; it may be oxidized, then conjugated and eliminated; or it may be partly detoxified and partly eliminated unchanged depending upon its reactivity. Acetanilide hydrolizes to acetic acid and aniline. The latter is oxidized to amino phenol, and excreted as such.

Detoxification occurs in the liver primarily, although the kidney and other tissues play lesser roles. The reactions may be facilitated and accelerated by naturally-occurring enzymes, such as the oxidases, esterases, and dehydrogenases. The rate of detoxification may be slowed or halted by large or very toxic doses of drug that are placed in the body. Some investigators believe that detoxification may be the accidental result of subjecting a reactive foreign substance to the naturally-occurring chemical reactions of the body, since some products are more toxic than their precursors. Acetyl sulphanilamide is more toxic than the original sulphanilamide. Amino phenol, which results from oxidation of anilin, is more toxic than the product from which it forms.

In studies of detoxification, many difficulties are encountered because mechanisms vary from one species to another and invalidate any application to man. Results vary also with the concentration, the mode, and rate of administration, and the absorption. There are two methods of approach in these studies, the direct, or chemical method, and the indirect, or pharmacological method. In the former, tissues, body fluids, and excreta are examined quantitatively. Micro-chemical methods are often necessary as the quantities involved are usually minute. In some cases where the amount of drug involved is small, the destruction is studied by perfusion experiments. In pharmacological methods, the rate of inactivation is determined without heed to the fate or type of destruction. Analeptics, barbiturates, and non-volatile drugs are studied in this manner (1).

Non-reactive drugs are not altered in the body but are eliminated unchanged according to their solubility, volatility, diffusibility, and other physical and chemical factors. Non-volatile drugs are eliminated through the kidney, gastrointestinal tract, and, to a small extent, through the skin. The elimination by the kidney depends upon the plasma concentration, blood flow, glomerular filtration, threshold level, and degree of tubular excretion. Diuresis may enhance the output. Volatile drugs are eliminated through the lungs, in addition to these other channels, depending on the vapor pressure and other factors.

Distribution varies with mode of administration. Inhaled drugs

are carried by the arterial blood to the tissues. Drugs administered orally, intravenously, rectally, and intramuscularly are carried to the right heart by the venous blood and mixed with venous blood from other parts of the body before distribution. The concentration in an organ depends upon the tissue solubility, the blood supply and the time after administration. Shortly after absorption, the liver, spleen, and other organs may contain large amounts. After a prolonged interval, the brain may contain more. Some drugs, after intravenous administration, are rapidly removed from the blood and accumulate in muscle and other tissue.

Inhalation anesthetic agents are chemically inert volatile substances (boiling point usually below 60° C.). Their elimination from blood is the reverse of absorption and depends primarily upon the coefficient of distribution, which is the ratio of a dissolved vapor or gas in a given volume of blood compared with an equal volume of air when the two are in equilibrium. Those gases which have low solubility co-efficients come to equilibrium with the partial pressure of the gas in the lungs sooner than those which are more soluble in the blood. During recovery, the gas tension in venous blood is higher than at the pulmonary alveoli, therefore the gas passes into the alveoli and the arterial blood leaves the lung with the same tension as the alveoli. The concentration at first falls rapidly, then slowly as the total remaining amount decreases. As a rule, those anesthetic agents requiring a high partial pressure for anesthesia, and having a low blood solubility, induce narcosis rapidly. Conversely where the solubility in the blood is high, and the partial pressure low, induction and recovery are slower. Early in the course of anesthesia, concentrations in the arterial blood are much higher than in the venous blood. After a variable period of time, the tissues approach an equilibrium with arterial blood and the tension in venous blood then approximates that of the arterial. Diffusion into and out of the tissue varies with the solubility in the tissue. Meyer, Overton, and others, found that anesthetic drugs have a high lipoidal solubility as compared with water. The ratio of the distribution in lipoid compared to that in water, when the two are in contact, is called the partition co-efficient. Those with high values are often termed lipophilic anesthetic agents. The fatty tissues absorb these freely. Although the tension of the anesthetic agent in the blood decreases rapidly during recovery, large amounts present in lipoid tissues may be slowly returned to the blood and complete body desaturation may require hours. Anesthetic agents which have a low partition co-efficient are more soluble in watery tissues, and equilibrium with blood saturation and desaturation are slower.

In addition to physical and chemical factors, certain physiological factors, the blood flow through the lungs, the pulmonary ventilation, and the blood flow through the different organs and tissues must be considered in absorption and elimination. Nervous tissue has the more

profuse blood supply and comes into equilibrium with the tension of the agent in the blood sooner than other tissues. Desaturation of nervous tissue is more rapid than other tissues during recovery and minute amounts of the drug may be present in the venous blood long after the subject regains consciousness. Depots of fatty tissue have a poor blood supply and consequently favor slow saturation and desaturation.

Mathematical expressions have been introduced by Haggard (2), Windmark (3), and others, to describe these physical-chemical relations to the elimination of volatile substances. These mathematical expressions, based on the forementioned factors, are too detailed for consideration here.

Individual anesthetics are best considered in their respective chemical groups. The volatile drugs are aliphatic hydrocarbons, alcohols, aldehydes, and ethers. Halogenated derivatives and ureides contribute the majority of non-volatile drugs. Nitrous oxide is the only important inorganic compound.

THE HYDROCARBONS

Hydrocarbons are chemically inert and have a low water and high lipoid solubility. The majority are volatile or exist as gases at ordinary temperatures. Saturated hydrocarbons have anesthetic properties, but are without clinical applicability. In the unsaturated group, the lowest member of the series, ethylene, is an anesthetic agent of merit. Its co-efficient of distribution for blood and air varies from 0.12 to 0.15 and the oil-water partition co-officient is 13. Nicloux (4) found elimination from the blood rapid with no detectable quantities of ethylene in the blood after two minutes. Complete desaturation, however, is slow since tissues, particularly lipoid tissues, retain appreciable quantities of the gas. Of the total carried by the blood 70–80 per cent. is in the cells. Diffusion through the skin varies, but may be as much as .0019 mgm. per sq. m. per hour.

Cyclopropane, the simplest member of the cyclic hydrocarbons, has both properties of a saturated and unsaturated compound. The blood-air distribution is 0.5, and the oil-water ratio 34.5. Partial pressure required for anesthesia averages 190 mm. Hg. Robbins (5) found the greater portion lost through the lungs in ten minutes, although detectable amounts were present in venous blood for several hours. Seevers et al (6) found that complete desaturation of tissues requires several hours. This finding is in conformity with the high lipoid solubility of cyclopropane. The concentration in venous blood equals that of arterial blood of the dog after fifteen minutes of anesthesia. Like ethylene, 80 per cent. of cyclopropane in the blood is carried by the cells. Very small amounts diffuse through the skin. Seevers recovered cyclopropane from the stomach of the dog.

The Alcohols

Two alcohols are now used for anesthesia, ethyl alcohol and amylene hydrate. Ethyl alcohol is oxidized by the body with the liberation of seven calories of heat per gram. Haggard and Greenberg (7) found as much as 8 per cent. of a total dose eliminated through the lungs. The pulmonary elimination follows closely the blood-air solubility ratio. Urinary excretion varies from 2 per cent. to 4 per cent. of the total amount ingested and parallels closely the plasma content of arterial blood. Bowman and co-workers (8) have recently observed that elimination from blood in acute alcoholism is accelerated by the simultaneous administration of insulin and glucose. Fifteen units of insulin administered intravenously with glucose in a concentration of 30 per cent. reduced the blood alcohol an average of 167 mgm. per cent. in two hours. In controls, or patients who received either glucose or insulin alone, the average was 54 mgm. per cent. during a like interval.

Tertiary amyl alcohol, commonly known as amylene hydrate, is used to prepare avertin fluid. Ordinarily, tertiary alcohols are not destroyed in the body. Data on the elimination of amylene hydrate are not in agreement. It is eliminated unchanged in the urine of man and dog. Some passes from the lungs. In the rabbit detoxification by conjugation with glycuronic acid occurs.

The Aldehydes

Free aldehydes are not used for anesthesia. Paraldehyde, a polymerization of three molecules of acetic aldehyde, has a cyclic structure, no free aldehyde group, and is relatively inert. Its fate is somewhat controversial. Recently Defandorf (9) working with dogs found 2.8 per cent. of a total dose was eliminated unchanged by the lungs and 1.3 per cent. in urine in seven hours. After twenty-four hours it was no longer detectable. The presence of a reducing substance in urine, suggested to him a conjugated product. In the rat, the drug is eliminated unchanged quantitatively through the lungs and urine. Paraldehyde is very soluble in water and in lipoid and has a low vapor pressure, boiling point 121° C. After intravenous administration the drug is found in various tissues, particularly the muscles and liver.

The Ethers

A number of ethers are known but only two are used clinically. They have a lower boiling point and solubility than their corresponding alcohols. Ethyl ether, which has a blood/air ratio of 15 to 1, and oil/water ratio of 3.5, requires a comparatively low vapor tension (35 mm. Hg) for anesthesia. Haggard (10) recovered 87 per cent. of the total from exhalation. Small amounts pass through the kidney, skin, and gastro-intestinal tract. Complete desaturation and elimination

are slow and require hours depending on duration and depth of anesthesia.

Divinyl ether is an unsaturated ether of the same carbon content as ethyl ether. Unlike ethyl ether the distribution co-efficient for air and blood is low and the oil-water ratio high. Ruigh (11) has shown the elimination to be similar to cyclopropane. Elimination from the blood is rapid, but complete desaturation of the tissues, particularly the lipoids, requires several hours.

HALOGENATED COMPOUNDS

Halogenation of hydrocarbons, aldehydes, and alcohols increases the potency of narcotic compounds. Brominated and chlorinated derivatives are more useful since iodine and fluorine are more toxic compounds having little narcotic potency. The prominent halogenated hydrocarbons are chloroform and ethyl chloride. Chloroform has an oil-water ratio of 100, a distribution ratio of 10.5 and requires a partial pressure of 5 mm. Elimination from blood is slower than other lipotropic substances. Tissue desaturation requires as much as six and one-half hours. Ethyl chloride is similar to chloroform but more rapidly eliminated from the blood.

Halogenated alcohols and aldehydes may be considered together since they are non-volatile compounds eliminated by conjugation. After ingestion of chloral hydrate, the urine contains a compound which yields glycuronic acid and trichlorethanol and is known as urochloralic acid. It is believed the chloral is reduced to trichlorethanol and conjugated with glycuronic acid. Studies on the elimination of trichlorethanol have cast doubt on this mode of detoxification. The duration of narcosis with trichlorethanol is longer than with an equivalent dose of chloral. As Lehmann and Knoefel (12) point out the hypnosis of chloral should be longer if the detoxification of chloral requires two steps in the body.

Tribromethanol, known as "avertin," is a non-volatile compound which combines with glycuronic acid and passes into the urine. After rectal administration of a therapeutic dose (80 mgm. per kilo), the blood level varies between 6 to 10 mgm. per 100 cc. during hypnosis. Gradually the drug disappears into the tissues, particularly nervous tissues (13). Elimination of the conjugated product by the kidneys is rapid and largely completed in four hours, although complete elimination may require from two to seven days. Bromine containing substances also pass through the skin. None is eliminated from the gastrointestinal tract or lungs (14). The conjugated product has no narcotic properties and the administration of glycuronic acid does not accelerate its formation. The more toxic aldehyde homologue, bromal, is also conjugated with glycuronic acid and eliminated in the urine.

NITROUS OXIDE

The elimination of nitrous oxide from the blood occurs in two or three minutes. The gas is very soluble in water and blood. Minute amounts are difficult to detect but it is believed small amounts circulate in venous blood several hours after anesthesia. The gas is stable in the body and does not yield nitrogen.

THE DERIVATIVES OF UREA

The usefulness of derivatives of carbamic acid (the urethanes), and the different substituted ureas which have hypnotic properties, is outshadowed by the more effective malonylureas, or barbiturates. The increasing and widespread use of intravenous barbiturates for anesthesia has centered attention upon the destruction of these drugs by tissues. A close relationship exists between chemical structure, narcotic potency, stability, and duration of action of the barbiturates. The barbituric acid molecule, formed by condensation of urea with malonic acid, is a six-membered ring upon which various substitutions and replacements may be made (15). The two hydrogens on the number 5 carbon are usually substituted by aliphatic radicals of variable carbon content. Those structures which have a total of two or three carbons result in drugs with low narcotic potency and a long period of action. As the number of carbons increases, the action becomes more intense and shorter in duration. Halogenation of these aliphatic groups, or the presence of an unsaturated linkage, increases the potency and shortens the period of action. An aliphatic group on a nitrogen increases potency and shortens the duration of action. Thiobarbiturates have a sulphur atom replacing the oxygen of urea. Longer-acting barbiturates, such as veronal and phenobarbital, are usually recovered in urine (up to 90 per cent. of the total ingested amount in a period of several days). Derivatives of higher molecular weight, such as dial, are more potent than veronal but, intermediate to shorter-acting drugs, may be partly recovered in the urine although they are largely destroyed in the body. Therapeutic doses of short-acting barbiturates, such as amytal, are destroyed in the body. In larger or toxic doses, some may be detected in urine. The exact fate of these drugs is not known but it is probable that the destruction varies with the type of drug. In the case of amytal, various degradation products have been isolated in urine, suggesting an opening of the ring with subsequent conversion of the compound to urea, carbon dioxide, and water. Degradation products of barbiturates with halogen groups on aliphatic substituents, such as pernocton, have been recovered in the urine. In these the ring structure remains intact, as suggested by the isolation of acetonyl maolnyl urea.

The short-acting N-methyl barbiturates, such as evipal, are rapidly destroyed. Weese recovered an unidentified barbiturate in the urine

which was approximately 1 per cent. of the total ingested dose. Long-acting N-methyl barbital and phenobarbital were found by Butler and Bush (16) to be demethylated to ordinary barbital and phenobarbital. Shorter acting derivatives were demethylated also, but their inactivation probably depends on breakdown of the ring after demethylation. Thiobarbiturates are destroyed rapidly. Pentothal, the most important and prominent of these, is so rapidly altered in the body that after ten minutes Kozelka and Hine (17) could not isolate it from any tissue. Veal and Reynolds (18) have demonstrated cumulative effects from repeated doses. The oxygen analogue, pentobarbital, is never recovered after the administration of pentothal. Kozelka et al ascribe these cumulative effects to intermediate degradation products. Destruction of barbiturates probably occurs in the liver since experimental poisoning of this organ converts therapeutic doses of short-acting barbiturates into long-acting ones. On the other hand, long-acting barbiturates, while not influenced by a damaged liver, are rendered toxic by experimental poisoning of the kidney. Little is known concerning the excretion and destruction of barbiturates in profound states of narcosis resulting from overdosage. Whether or not toxic effects of drugs further contribute to the symptoms by preventing destruction remains to be determined. Recent work indicates that barbiturates may be destroyed by blood plasma and muscle tissue. Delmonico (19) reports no change in the dose of pentothal in patients with hepatic damage as compared to subjects with normal liver function. He suggests destruction by these other tissues. After an intravenous administration of a barbiturate, the drug disappears from the blood into various tissues in amounts dependent upon the blood supply of the organ and the solubility of the barbiturate in the particular tissue. More is found in the central nervous system because of the high lipoid solubility. Distribution in nerve tissue is fairly uniform with no localized accumulations in various anatomical divisions. As the tissues absorb the barbiturate, the blood concentration falls rapidly, but small amounts are detectable in the blood as long as the drug is still present in the tissues. The concentration in the spinal fluid is very small. Kozelka and Tatum (20) were unsuccessful in detecting appreciable quantities in spinal fluid of man even after large doses. One liter of fluid pooled from many patients contained one milligram.

THE LOCAL ANESTHETICS

With the exception of a number of aromatic alcohols for topical use, local anesthetics are synthetic basic compounds with many characteristics of the alkaloids. The better known and more widely used derivatives are esters whose destruction occurs in the liver by hydrolysis. Procaine is easily hydrolized into paraminobenzoic acid and the complex diethylaminoethanol. Cocaine, double ester of benzoic acid and

ecognine, and methyl alcohol, is less easily hydrolyzed and the greater portion is eliminated unchanged. Individual local anesthetics are so numerous that information on the elimination and destruction of each individual drug is lacking. However, with experimental poisoning of the liver, toxicity of most local anesthetics is increased, suggesting that this organ plays the important part in the elimination and destruction of the group as a whole. Dunlop (21) demonstrated the destruction of procaine by other tissues but concluded that the liver accounts for 95 per cent. of the total destruction.

Opiates and Other Alkaloids

The twenty-five or more alkaloids derived from opium may be grouped chemically into those derived from isoquiniline and those derived from phenanthrene. In the former, the more important papaverine is little used by anesthetists. In the phenanthrene group, two alkaloids are widely used—morphine and codeine. A synthetic derivative, dilaudid, is also popular. Morphine is detoxified in the body since less than 15 per cent. of a total dose is recovered free in urine. Recent work (22) suggests that detoxification may be by conjugation. After extraction of free morphine from urine, subsequent acid hydrolysis yields more morphine. Following intravenous administration, the concentration in blood falls quickly and only minute amounts are detectable after 10 minutes. The greater portion is distributed to muscle and liver tissue. Codeine, which is morphine, with methylation of the phenolic hydroxyl, is less readily attacked in the body. As high as 85 per cent. of a therapeutic dose may be recovered in urine.

Various non-narcotic alkaloids and synthetic drugs are constantly used by anesthetists to stimulate the central or sympathetic nervous system or to paralyze the parasympathetic system. Two alkaloids used to paralyze the parasympathetic system are atropine and scopolamine. These chemically related drugs are esters of tropic acid. Atropine is a racemic mixture of tropine tropate. Scopolamine is a levo scopine tropate. They are partially hydrolyzed, probably by the liver, but may be recovered in minute amounts in the urine for as long as thirty-six hours after therapeutic doses. Enzymes have been demonstrated in livers of rabbits and guinea pigs which hydrolyze these esters completely (23). Their existence in man is not known.

Analeptic Drugs

A number of drugs widely used to antagonize the action of narcotics or to exert a stimulating effect on various organs are of interest.

Metrazol (pentamethylene tetrazol) consists of a 4-Nitrogen ring fused with a 6-Carbon ring. It is not destroyed by liver tissue (24). In its passage through the liver, two molecules combine forming a compound which does not respond to usual tests for the drug. This substance passes into the urine.

Picrotoxin. The chemical structure of picrotoxin is not established. The molecule yields two portions: a non-convulsive substance, picrotin, and a toxic product, picrotoxinin. The toxicity of the latter is twice that of picrotoxin. Dille (25), in studying the inactivation and elimination in rabbits, found a single convulsive dose to be inactivated in one and a half hours. A convulsion-producing substance could be detected in the urine eighteen hours after one convulsive dose in the rabbit.

Coramine, the diethyl amide of beta pyridine carboxylic acid, was found by Werner and Tatum (26) to be inactivated more slowly than either metrazol or picrotoxin.

Caffeine (trimethyl xanthine) is destroyed by demethylation and finally converted to urea. In larger than therapeutic doses it may appear in an unchanged form or as partly demethylated degradation products in the urine.

Camphor, a cyclic ketone, is reduced to a secondary alcohol, and detoxified by conjugation in the liver with glycuronic acid. The product is passed into urine.

Ephedrine, unlike its pharmacological ally, adrenalin, which is rapidly destroyed by the oxidases of blood and tissues, is comparatively stable. This stability may be the explanation for its sustained action. In perfusion experiments, ephedrine was detectable three hours after administration. The exact fate of ephedrine in man has not been determined (27).

SUMMARY

The chemical mechanisms for destruction of anesthetic agents in the body are reviewed.

Inhalation anesthetics are chemically inert and eliminated mainly through the lungs. Their elimination is the reverse of absorption and follows certain physical and chemical laws.

Not volatile drugs may be subjected to various biochemical mechanisms of the body and converted to compounds with less physiological activity. These reactions occur most frequently in the liver and are termed "detoxifications."

The exact fate of many drugs is not known. The rate of inactivation is studied and serves as a guide in these cases.

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ERRATUM

The following reference should be included with those of the article by Ernest H. Warnock, M.D., and Ralph M. Tovell, M.D., which appeared on pages 187–204 inclusive of the September issue of ANESTHESIOLOGY.

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THE SUBSTANCES CAUSING VASOCONSTRICTION

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Epinephrine

The name epinephrine was applied by Abel to the active principle which he isolated in 1897 and which was subsequently found to be a benzoyl derivative (1). This name was adopted by the American Medical Association in place of the protected name adrenaline.

The first of this group of substances was revealed by the experiments of Oliver and Schäffer (2) in 1894 with extracts of the suprarenal glands. In 1901 Aldrich and Takamine isolated the active principle and named it adrenaline. Friedmann in 1906 obtained its structural formula. It was synthetized by Stoltz and Dakin in 1905. The studies of these workers made evident that other chemically related bodies produced more or less similar actions as did those of Barger and Dale (3).

Oliver and Schäffer showed quite clearly that an extract of the suprarenal glands caused contraction of the arteries and led to an increase in the beat of the auricles and ventricles. They further showed that the effect of the active principle was peripheral upon the organs themselves and not due to an action on the central nervous system.

In the thirty-five years that have passed since the publication of their main paper, it has been established that the amount of epinephrine present normally in the blood stream is extremely small; how small we do not know. The figures of Stewart and Rogoff would suggest about 0.002 mgm. in the blood of a man, and it has been shown that its presence is not necessary to maintain the blood pressure. It may be that even this small amount has some importance in cardiac metabolism, allowing the heart to do the same amount of work with a lower consumption of oxygen, as suggested by Gremels (4), who found this to occur when from 0.0026–0.008 gamma per kgm. per min. of epinephrine was infused into a cat. In his experiments, increasing the amount three times led to an increased consumption of oxygen, but even this amount is far smaller than that which may be released in the dog by stimulation of the sciatic nerve. Cannon (5) estimates that in fright, pain and asphyxia, as much as 0.001 mgm. per kgm. body weight per minute may be released reflexly from the gland. This result is approximately what might be expected from the intravenous injection in man of 0.5 cc. epinephrine hydrochloride, when a rise in blood pressure would occur. Samson Wright (6) reports that if 1.5 cc. of the solution of epinephrine hydrochloride be injected subcutaneously in man, it will produce an increased cardiac rate with increased minute volume, but with no in-

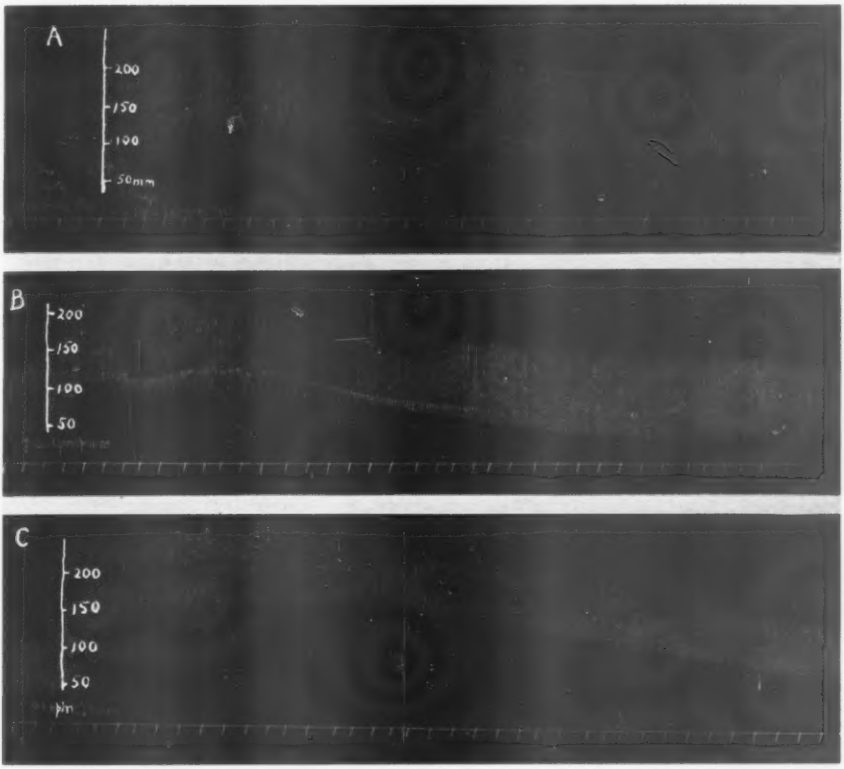
crease in pressure, as the opposing reflexes are able to offset any vasoconstriction. The oxygen consumption will, however, increase some 20 per cent. Absorption from a subcutaneous injection of 0.5 cc. usually will not give a concentration of epinephrine adequate to overcome the controlling reflexes and frequently will produce no increase in cardiac rate, while a smaller amount administered intravenously will do so. The anesthetist is concerned with the use of epinephrine to produce a concentration either equal to what may be produced reflexly, or in some cases, somewhat larger quantities, and not with concentrations such as those that produce the usual textbook picture.

Indeed, the usual textbook picture of the abrupt rise of blood pressure from normal to 75 to 150 mm. Hg above normal, with its almost equally prompt fall, reaching the normal level in two minutes or so, conveys a totally erroneous picture of the action of epinephrine used therapeutically. In such a case the high pressure throws an undue strain upon the heart which, owing to its wasteful use of oxygen, it cannot master. The abrupt fall is in part an expression of its failure to cope with an impossible effort.

Let us consider rather the effect of a lesser dose administered by intravenous injection. The epinephrine produces a vasoconstriction in the arterioles of the skin and splanchnic area. The constriction reaches its maximum in a few seconds after reaching the vessels, and is maintained for some minutes. The rise in diastolic pressure leads to decreased cardiac emptying, decreased stroke volume and pulse pressure. The blood not ejected with the normal inflow increases the diastolic length of the fibres and leads to gradually increasing stroke volume and pulse pressure. This phase lasts again a few seconds. Then another factor intervenes; namely, an increased venous return. The spleen constricts due to the effect of the epinephrine, as do certain of the larger abdominal veins. Possibly in man, as in the dog, some blood is released from the liver. A little blood is transferred from the contracting vessels to the venous side. The increased venous inflow again stretches the ventricular fibres, and an increased stroke volume and pulse pressure results with a further rise in mean pressure. The epinephrine causes a dilation of the coronary arteries, and with the increased pressure, a much greater blood flow, with increased supply of oxygen to furnish cardiac energy. The increased pressure has enhanced the flow through the cerebral circulation and that of the muscles, and even through the constricted vessels the flow may be increasing. A more or less great increase in rate of circulation occurs so that there is increased flow through the pulmonary arteries and increased oxygen supply per minute to the body and increased venous return to the left heart, with increased minute volume and a further rise of pressure. This whole sequence of events requires perhaps a minute.

This description is again abnormal, though it may occur under certain anesthetic conditions when the centres in the medulla are de-

pressed. Usually we find in animals, and this occurs in normal man, that the initial rise in pressure in the carotid sinus and in the arch of the aorta sets into activity the pressor sensory receptors and volleys of impulses are sent via the glossopharyngeal and the vagus nerves to the cardio-inhibitor and the vasomotor centres. Their altered activity leads to a decreased cardiac rate and some vasodilation, particularly in vessels not strongly constricted by epinephrine itself. In this case, after the primary rise in pressure due to vasoconstriction, the cardiac rate decreases, diastolic pressure tends to fall, the heart has a longer



A. Dog, 20 kg., under morphine and light ether. B.P. written with a tonometer giving pulse pressure values. Mean B.P. rose from 140 mm. Hg to 175 mm. after an intravenous injection of 0.1 mgm. of Epinephrine Hydrochloride. Note the marked decrease in pulse rate due to carotid and depressor reflexes. Vaosdilation undoubtedly also occurred. Pressure reached normal level again in 105 seconds. *B.* Now under very deep ether. B.P. lower, 85, rising to 155. Cardiac reflexes less marked. Rise lasts 140 seconds and the pulse pressure is still above normal at this time. *C.* High spinal anesthesia has now been added. No cardiac reflexes are apparent. B.P. rose from 72 to 215 mm. and lasted 225 seconds. In this tracing the two stages in the rise of pressure are very evident. The first is due to the vasoconstriction only and is accompanied by a decreased stroke volume and pulse pressure. Then an increased venous inflow from spleen, liver, veins and constricted vessels and the increased circulation rate occurs with increased stroke volume and pulse pressure.

interval to fill and the stroke volume is increased. Then the increased venous inflow from spleen, veins, and liver, takes effect and the stroke volume increases further. Again, the flow through the coronaries increases, as does that through the cerebral and vessels within the muscles, even though the blood pressure rises some 20–30 mm. Hg. The rate of circulation usually increases and so does the minute volume. A redistribution of the blood in circulation thus occurs. This is similar to the effect produced by pain or fright when the blood pressure may not be raised greatly, and it approximates the effects of a subcutaneous injection described by Samson Wright and referred to above. Even when in this case blood pressure has fallen to its normal level, the redistribution still exists and the complete return to normal outlasts the increase in pressure.

But the anesthetist rarely employs epinephrine when the blood pressure is normal but only when it has fallen, due to either vasodilation or cardiac failure. Let us consider the case where the fall is due to vasodilation. As before, epinephrine causes vasconstriction, increased pressure, in a few seconds increased venous return, increased stroke and minute volume and increased rate of circulation, but as long as the mean blood pressure does not much exceed the normal, the carotid sinus and depressor reflexes of the aortic arch do not exert much effect. The decreased cardiac rate does not occur. Indeed, the rate may be increased (*a*) by the effect of epinephrine on the sinus node and (*b*) by the increased venous pressure setting up the Bainbridge reflex. In animals in such a case the rise of pressure may last eight or ten minutes.

Even more favorable conditions exist when the vasomotor and cardio-inhibitor centres are depressed by some drug. Here again the rise of blood pressure with its attendant redistribution of blood and increased circulation rate may last much longer. Indeed, a pressure slightly above normal may last for 10–15 minutes. If the original cause of the low pressure has been due to depression of the vasomotor centre caused by a drug, the increased cerebral blood supply may aid in removing the cause.

As is well known, even in the case of the decrease in pressure being due to a cardiac failure, the patient may be saved by an intracardiac injection of epinephrine. Some 0.3 cc. of the Liquor Epinephrinae Hydrochloridi, preferably diluted with some 25–50 cc. of saline, should be injected into the left ventricle, the object being to have some enter the coronary arteries and so reach the sinus node and the musculature. Epinephrine increases the activity of the node and increases the contractility of auricular and ventricular muscle. Not only this, but as the epinephrine reaches the coronary vessels they will dilate, and with the recovery of arterial pressure, the heart will again be supplied with blood and oxygen. It is evident from the cases reported by Asteriades (7) and others that this use of epinephrine may be effective even in the case of cardiac failure under chloroform.

Under spinal anesthesia an abrupt fall in pressure may occur. Whether one agrees with Smith, Rovenstine, et al (8), who claim that the blocking of the sympathetic fibres, which go to make up the major and minor splanchnics which supply the vasoconstrictor fibres to the viscera and of those which supply the vessels of the lower limbs, does not lead to a dilation of the vessels in these areas, or with those who claim that these vessels must dilate as they are receiving normally a tonic vasoconstrictor supply, it must be realized that the mechanisms for the maintenance of a normal blood pressure have been interfered with. Normally a fall of pressure at the carotid sinus and aortic pressure endings leads reflexly to increased cardiac rate, vasoconstriction and to release of epinephrine from the adrenals. Yet in the case of a high spinal anesthetic the sympathetic pathways to the spleen, the adrenal and to the vessels of the lower limbs and viscera are blocked. Only the increase in cardiac rate and constriction in relatively minor vascular areas are available. The normal or increased blood flow to the heart and brain which these reflexes strive to maintain cannot be accomplished. It is quite obvious that here there are indications for the use of epinephrine.

SURGICAL SHOCK

In the case of true surgical shock there is not the same justification for the use of epinephrine as in other cases of low blood pressure. Here the fall of pressure is due to the escape of fluid from the capillaries. This loss of fluid will be accompanied by a fall of pressure and this in turn will lead to reflexes from the carotid sinus and aorta resulting in vasoconstriction and secretion of epinephrine. The arterioles will be constricted. Only when the adrenal medulla was exhausted could there be an indication for the use of epinephrine, and then in very low physiological concentration which might do nothing more than improve cardiac contractility.

ETHER

When ether is administered, it is known that cardiac rate is increased, blood pressure rises, minute volume increases and the value for blood sugar increases. Hence many persons have inferred that this is due to a liberation of epinephrine. Indeed, Elliott (9), Fujii (10) and Kodama (11) and others have shown that content of epinephrine in the adrenal gland falls during an ether anesthesia. It has, however, not been proved that the increase in heart rate, the increase in blood sugar and circulation rate are entirely due to a release of epinephrine either reflexly or due to the action of the ether on the adrenals, but may be due to the action of ether elsewhere as Heymans (12) has shown that the increased heart rate may be explained on the basis that ether depresses the mechanism of the carotid sinus.

In conclusion, one should refer to the use of epinephrine with local anesthetics, where the great advantage lies in the constriction of the

minute vessels, and consequently the decreased circulation leads to a slower fall in the local anesthetic concentration and an increased duration of anesthesia. It seems a common misapprehension that the small amounts of epinephrine escaping from the area will have no effect. It is true that the concentration of epinephrine in the injection is low—1:50,000–1:100,000—but if the total injection is large some will escape. It is well known that a subcutaneous injection will relieve the itching in urticaria or an attack of asthma. Those who use it for these purposes are aware that there may be some palpitation and discomfort even if the blood pressure does not rise. The epinephrine has, in part, left the site of injection and has reached the bronchi, the skin and the heart. The reflex mechanisms, however, succeed in confining the rise of blood pressure to less than 10 mm. of mercury. It may be that the concentration of epinephrine in the blood stream has not reached a sufficient concentration to give an effective vasoconstriction, while it has been ample to dilate the abnormally constricted bronchi.

CONTRAINDICATIONS

As we have noted, epinephrine administered even in low concentration changes cardiac metabolism, and in the ordinary therapeutic dose intravenously or subcutaneously, it also produces changes in cardiac function. Levy (13) showed that in light (non-surgical) chloroform anesthesia in cats an injection of epinephrine led to sudden ventricular fibrillation and death. In dogs the effect is not so marked, as judged by the work of Meek, Hathaway and Orth (14), as in none of their animals did fibrillation occur, but in a large percentage ventricular extrasystoles, and in about 10 per cent. ventricular tachycardia of short duration, did occur. Cyclopropane, like chloroform, may cause extrasystoles, and again the above authors have shown that epinephrine caused, in dogs subjected to cyclopropane anesthesia, an even higher percentage of ventricular tachycardia and of ventricular extrasystoles. Consequently it is probably not wise to administer epinephrine to patients under cyclopropane. Against this must be set the fact, as mentioned above, that patients have been given epinephrine in cases of cardiac failure under chloroform.

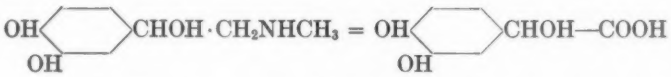
MODE OF ACTION

The work of Loewi and Cannon has made it clear that the stimulation of a sympathetic nerve leads to the liberation of an epinephrine-like substance "sympathin" and that this unites with the cell, causing its activity or depression. There is still a dispute as to whether sympathin or epinephrine is liberated and unites with the cell and also, as Cannon's school have shown, it may be carried away by the blood stream and increase the activity of other cells. Hence it seems reasonable to suppose that injected epinephrine also unites in some manner

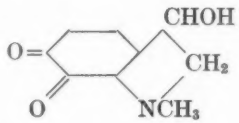
with the cells it activates or depresses. It has also been abundantly shown by Meltzer and Auer and many other workers that epinephrine produces its characteristic effect after sympathetic nerve fibres to the organ have degenerated.

Straub has proposed the theory that the action of epinephrine only occurs while it is entering the cell, and that once the internal concentration equals that externally, the action ceases. He takes it for granted that epinephrine is rapidly destroyed intracellularly. This would, in his opinion, account for two well established facts. First, that very soon after the action of any reasonable dose of epinephrine is over, another dose of the same size gives exactly the same effect. Secondly, that blood pressure can be maintained in the completely pithed animal at any desired level by a constant intravenous infusion.

The chemical structure of epinephrine makes it liable to destruction in various ways. Blaschko has isolated an enzyme, amino oxidase, which attacks a terminal amine NH_2 group and in the case of tyramine parahydroxyphenyl acetic acide is formed. Were merely the same effect produced with epinephrine,



the change, as shown above, would take place and activity would be lost (Blaschko (16) 1937). But in the body there is a much more common oxidative system, the so-called cytochrome system, and this transforms epinephrine into adrenochrome.



This requires the uptake of two atoms of oxygen with the loss of activity and the formation of a red compound (Green and Richter (17)).

Atmospheric oxidation of adrenaline leads to a loss of activity with the uptake of two atoms of oxygen. This reaction is prevented from taking place by the presence of ascorbic acid, glutathion and amino acids (18). It will not account for the loss of epinephrine in the body. Possibly the cytochrome oxidation is also interfered with by ascorbic acid.

It would seem that Blaschko's enzyme which is abundant in the liver is the most likely mode of the destruction of circulating epinephrine, but it is as yet not clear what happens to epinephrine when it becomes attached to tissues. There is no doubt, as pointed out above, that Blaschko's enzyme will destroy the activity of tyramine, epinephrine, epinine and dihydroxyphenylethylamine readily, all other members of the ethanolamine group, sympathol (meta or para), arterenol, adrena-

lone less readily, and will unite with, but will not destroy, or will destroy only extremely slowly ephedrine, corbasil, and colephrine. This is probably true of the other members of the propanolamine group (Blaschko). It seems at the present probable that some similar enzyme system destroys epinephrine after it has become attached to cardiac and vascular muscle cells.

EPHEDRINE

Although Nagai in 1887 isolated this alkaloid from Ephedra vulgaris, it was not until the work of Chen and Schmidt (19) that its importance became recognized. Their studies showed that ephedrine produced a rise in blood pressure, an increase in cardiac rate and contractility and raised the blood sugar. The rise in blood pressure, like that of epinephrine, is primarily due to contraction of arterioles in the skin and splanchnic area, a contraction of the spleen and veins (Mugge (20)), to which is added the increased cardiac contractility, if moderate doses are used. Of these effects, that on the vessels seems to be less marked than with epinephrine, while that on the spleen is more marked (Mugge). The whole rise of pressure lasts several times longer than that produced by epinephrine. Cardiac rate appeared to be more frequently increased. The effect was clearly shown to be peripheral, as it occurred in the completely pithed animal. Ephedrine produced, indeed, effects resembling epinephrine, but from the first, certain differences were observed. (*a*) The effects of ephedrine lasted longer. This we now know is due to its less rapid destruction by the liver. This also is the reason why it has relatively much more effect when given subcutaneously, and even more when given by mouth, than has epinephrine. (*b*) The studies of Schaumann (21), Kreitmair (22), Hildebrandt (23), and Mugge (20), showed that it produced relatively little effect on perfused vessels. (*c*) A second dose, administered after the effect of the first had declined, produced less effect, and succeeding doses still less (a phenomenon now termed tachyphylaxis). This is not due to an immunity, for Rühl (24) showed that rabbits injected daily for months still showed the characteristic effect. (*d*) Schaumann showed that in the perfused frog's vessels the vasoconstrictor effect of epinephrine was greatly increased by a previous apparently ineffective dose of ephedrine. Csepai and Doleschall (25) in 1925 showed that after ephedrine, epinephrine produced a greater effect in man. Finally, Burn (26) showed clearly that ephedrine was without arteriole effect, save when circulating epinephrine was present. Meantime, Blaschko's enzyme had been studied, and as it has been shown that this enzyme united with ephedrine but did not destroy it, Gaddum (28) has urged the theory that ephedrine, by poisoning this enzyme (as eserine does the choline esterase), leads to circulating epinephrine (or sympathin), being adequate to produce the vascular contraction which in turn produces the rise in pressure. Gaddum then explains the tachyphylaxis by

ephedrine uniting with the vascular cells, but without obvious effect. The cell receptors with which the ephedrine unites are, Gaddum assumes, those with which epinephrine also combines, and hence the lessened effect of repeated doses, as less epinephrine can unite with the cell. Gaddum and Kwiatkowski (27) showed that even with the isolated perfused rabbit's ear, ephedrine, while it alone produced no vasoconstriction, greatly increased the effect of subsequent doses of epinephrine, as the presence of ephedrine prevented the destruction of the epinephrine. They further showed that sympathetic stimulation of the vessels of the perfused ear led to a larger amount of sympathin or epinephrine being liberated into the perfusing solution than occurred previous to its administration. Unfortunately, Richter and Tingey (29) have shown that epinephrine, in the concentration prevailing in Gaddum's experiments, is very slowly destroyed by Blaschko's enzyme, and that ephedrine in the concentrations present in Gaddum's experiments did not inhibit the enzyme. They further failed to find any enzyme in the macerate from the rabbit's ear. They also point out that the chief source of this enzyme is the liver.

The total evidence, however, does suggest that ephedrine depresses whatever enzyme system normally destroys epinephrine, though this may not be Blaschko's enzyme.

The other explanation of subsequent doses of ephedrine not producing the full rise of pressure produced by the first, raises a more serious point in the action of ephedrine. This explanation depends upon experiments which appear to show that ephedrine has a deleterious effect upon the heart. Both theories have in common the assumption that ephedrine, after union with the cell, is very slowly destroyed or removed. This assumption seems justified by such work as that of Kreitmair, who showed that after a single moderate dose of epinephrine, the effect of a given dose of epinephrine was increased for two hours or more. The evidence of cardiac damage was inferred by Schaumann, and is strongly stressed by Hildebrandt and by Mugge. The experiments of these two workers showed that a first moderate dose of ephedrine increased the cardiac contractility slightly and increased the coronary flow, while repetitions of such injections led to a definite decrease in coronary flow and progressive cardiac failure, probably in part dependent on the decreased flow. Larger doses of ephedrine led from the first to cardiac dilation.

Further, we have evidence of some direct cardiac effect of ephedrine in the work of Meek and Seevers (30), who refer to other less thorough studies of the same kind. These authors studied the effect of doses of ephedrine from 0.5–20 mgm. per kilogram (1 milligram per kilogram would correspond approximately to the dose given before spinal anesthesia in man). In all dogs but one there was an initial bradycardia with doses of 1–20 mgm. This is doubtless due to a carotid sinus reflex. This reflex may lead also to extrasystoles and slow ectopic rhythms.

But ephedrine also stimulated the lower automatic centers and, if this effect is marked, extrasystoles or tachycardia may occur.

In these papers there is evidence that there is an optimal favorable initial dose of ephedrine and of the accumulation of repeated small doses until an optimal effect is obtained. The evidence may then be drawn together as follows: Ephedrine has little effect upon vessels and the effect it apparently produces is due to circulating epinephrine. This causes the primary coronary dilation, the constriction of the spleen which, according to Mugge, outlasts the constriction of the arterioles, and of the veins which is even longer-lasting, but the union of the ephedrine with the cells of these structures prevents or decreases the entrance of epinephrine when present in merely the normal circulating concentrations, but will not prevent higher concentrations, as obtained by injection, having an even increased effect, until the amount of ephedrine is such that epinephrine causes vasodilation or cardiac failure, and either owing to a direct effect of ephedrine on the coronary vessels or on the heart muscles, decreases cardiac contractility.

EPHEDRINE IN MAN

Chen and Schmidt found that 40–60 mgm. intramuscularly produced rises in blood pressure of 20–30 mm. Hg, with a decreased heart rate, while 60 mgm. per os produced a rise in one case from 128/60 to 150/68, with a decrease in pulse rate from 74 to 60. The effect began in about 30 minutes and lasted for two hours.

Foged (31) found that doses per os of 1.4–2.0 mgm. per kilogram (i.e. from 84–120 mgm. for 182 lb. man) produced rises of pressure of from 10–35 mm. Hg in different cases. The maximal rise occurred in 30–90 minutes. Intravenously 1.3–2.0 mgm. per kgm. produced rises in various cases of 30–60 mm., the maximal effect occurring in 20–60 minutes with a gradual decline for 2–3 hours. Similar results are reported by Oremus.

Csepai and Doleschall found again that 10 mgm. of ephedrine intravenously produced rises in blood pressure 10, 12 and 35 mm., while 0.01 mgm. of ephedrine intravenously produced a 10, 15 or 35 mm. before ephedrine; after ephedrine the same amount produced increases of 22, 40 and 95 mm.

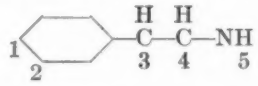
The larger doses lead to a decrease in anesthesia and the production of restlessness, tremor, perspiration, warmth or chilliness and gastric distress.

From the above evidence certain important conclusions may be fairly drawn. If ephedrine has been given in an adequate dose of 50–100 mgm. its effects will last for an hour and a half or two hours, at least. Epinephrine given during this time will have more than its usual effect and the effect will last longer. Further, the effectiveness of ephedrine depends on circulating epinephrine and if the circulating amount of this hormone be less than normal or even absent, as it well might be if

the innervation of the adrenals had long been blocked, epinephrine should be given with or before ephedrine. Even a subcutaneous injection of epinephrine, which normally would produce no effect, would be adequate to make ephedrine effective. But all in all it is evident that epinephrine is a more valuable agent than ephedrine, though the latter may be used to prolong the effect of the former, and for this purpose quite small doses of ephedrine, 25–50 mgm., are probably adequate.

OTHER MEMBERS OF THIS GROUP

It will save a great deal of repetition if the differences in the structures of the epinephrine and ephedrine molecules are understood. The first difference lies in the absence of the two hydroxyl (OH) groups on the phenol ring in ephedrine. This probably contributes to its stability. The second lies in the fact that there are three carbon atoms in the chain preceding the NH_2 group. In other words, the side chain in ephedrine is a propanolamine one, while in epinephrine it is an ethanolamine. We can, indeed, divide the members of this general group into these two classes and the structure of those that will be discussed is shown schematically in the following Table.



Numbers of Places Substituted	1	2	3	4	5
Epinephrine. Adrenaline	OH	OH	OH	H	CH_3
Sympathol. Synephrine	OH	H	OH	H	CH_3
Meta Sympathol. Neosynephrine. Adrianol	H	OH	OH	H	CH_3
Epinine	OH	OH	H	H	CH_3
Arterenol. Noradrenaline	OH	OH	OH	H	H
Ephedrine	H	H	OH	CH_3	CH_3
Corbasil. Cobefrin desoxy-norephedrine	OH	OH	OH	NH_2	CH_3*
Veritol	OH	H	H	CH_3	CH_3
Suprifene	OH	H	OH	CH_3	CH_3

* Replaces the NH_2 group.

It should be remembered that the occurrence of two hydroxyls in the phenyl ring, as in epinephrine, epinine and arterenol, lead to a more rapid destruction and a less sustained action; that the presence of only one hydroxyl decreases the potency but lengthens the action.

Further, the members of the propanolamine group are not appreciably destroyed by Blaschko's enzyme and have a more prolonged but weaker action. In sufficiently large doses they would be expected to show tachyphylaxis, but not all members do so as is mentioned below. They will all potentiate the effect of epinephrine.

SYNEPHRINE. SYMPATHOL

This epinephrine-like substance, as many of the others, was studied first by Barger and Dale (3). Given intravenously it produces a prompt rise of blood pressure, but a dose some 50 times larger than that of epinephrine is required. The pressure remains elevated for a longer time—20 minutes. The rise is due to an increased venous return from the spleen and liver, and to some vasoconstriction of arterioles in skin and muscle and probably veins (Hochrein and Keller (33)). The coronaries are dilated (Ruhl (34)) but apparently less so than with epinephrine (Gremels (35)) and cardiac irregularities are not so readily produced as with the latter. The effect of synephrine on heart rate is much less than with epinephrine (Tainter and Seidenfeld (36)) but cardiac contractility is improved. While according to Ruhl epinephrine clinically is of most value in improving cardiac activity, synephrine is also of value and according to Gremels may be of more value as it does not increase the oxygen requirement of the heart so much. Synephrine is more stable in solution than is epinephrine (Ehrismann and Maloff (37)). It constricts perfused vessels (Tainter and Seidenfeld) and repeated injections produce equal effects. Hyperglycemia is far less than that produced by epinephrine (Pflug and Brentano and Pflug (38)). Ruhl states that the most useful dose for man is 100–150 mgm. intramuscularly. It is much less effective per os. In emergency such a dose may be given intravenously.

NEOSYNEPHRINE. META-SYMPATHOL. ADRIANOL

The study of metasympathol has shown that it has only about 1/15 of the effectiveness of epinephrine in raising blood pressure when given intravenously, but its action lasts longer and it is not so apt, when producing a moderate rise of pressure 30–40 mm. Hg, to produce extrasystoles or manifest a deleterious cardiac effect. Subsequent doses do not exhibit a decrease in its effectiveness (Kuschinsky and Overdisse (39), and Johnston (40)). As is to be expected, it shows little evidence of central action, and patients do not show the restlessness, tremor or decrease in anesthetic depth that may occur with ephedrine (Brunner and de Takats (41), and Johnston). The rise of blood pressure produced by subcutaneous or intramuscular injection appears in doses of 5 mgm. to be about 30 mm. Hg, but varies greatly from 0–70 mm. The pulse rate is usually decreased, e.g. 102 out of 114 cases (Lorhan and Lalich (42)). In some there may be an increase. The rise of pressure after intramuscular injection begins in about 4 minutes, lasts about 45 (Tainter and Stockton (43)). About 5 mgm. subcutaneously or intramuscularly per patient may be considered a usual prophylactic dose in spinal anesthesia (Bittrich (44), Johnston, Brunner and de Takats, Lorhan and Lalich). In some cases irregular hearts become more regular and this is compatible with the observations of Kuschinsky and

Overdisse, that neosynephrine has less deleterious effect than epinephrine. It seems from their work and that of Gremels that synephrine is even more likely to improve cardiac action. It must be remembered that overdoses may produce some deleterious effect on cardiac action (Charlier (45)). This drug has, therefore, certain advantages over epinephrine, namely it is less likely to produce cardiac irregularity of a serious type (i.e. those not due to reflex bradycardia or nodal rhythm but due to a stimulation of subordinate pacemakers). It does not decrease the effect of premedication, but on the other hand it does not produce the prolonged effect of ephedrine.

Epinine has apparently been very little studied. Its action seems to resemble closely that of epinephrine but is not more than one-seventh as potent but its effects last a little longer (Barger and Dale). It is destroyed by Blaschko's enzyme.

ARTERENOL

This substance is the only member of the series which is more active than epinephrine (50 to 35, Barger and Dale; 50 to 40, Tainter (46)) and its effect lasts a little longer.

VERITOL

Veritol has been subjected to a great deal of study in Germany and has been used in connection with spinal anesthesia, both prophylactically as ephedrine is given and during a fall of blood pressure (Kreise, Garan et al (47)), but these authors found it of no value in severe circulatory collapse. As pointed out above it produces a prompt, long-lasting rise in pressure. It is more potent than synephrine but its effect does not last quite as long as ephedrine (Grosse-Brockhoff and Kaldenberg (48)). The effects on blood pressure occur in the fully pithed animal (Eichler (52) and Lindner (51)). In animals an examination of its action has shown that an increased venous inflow due to the contraction of the spleen (Rein (49)) and from skin and muscles (Zipf (50)) is the first cause of the rise of pressure; to this is added a less marked vasoconstriction elsewhere. Its effect on perfused vessels, like ephedrine, is slight or absent (Lindner). The cardiac contractility seems to be improved. When the heart has been poisoned, veritol distinctly improves its action (Rein, Zipf and others). If large doses are used, a second one has less effect. This is in part due to the contraction of the spleen persisting after blood pressure has fallen to normal; in part due, doubtless, to the reasons advanced in the case of ephedrine. Coronary flow is increased but not as much as with epinephrine. Oxygen consumption for the work done by the heart is decreased by small (Rein), not by large doses.

These effects have been confirmed in man (Sturm and Voges (53)) with 10 mgm. doses intramuscularly. Such a dose produced no un-

toward symptoms, while 20 mgm. caused vomiting, headache, dizziness, cold feet and hands. Other authors noted extrasystoles, Parade (54) with 4 mgm. and Köhler (55) with 20 mgm. in some cases. With higher doses they apparently occur more frequently (Aschenbrenner and Codas-Thompson (56)). It has little effect per os unless large doses, 60 mgm., are used (Reindell, Baurhenn, and Braunbehrens (57)). Ten mgm. subcutaneously or intramuscularly will increase the systolic blood pressure from 20–70 mm. Hg in 30–40 minutes (Sturm and Voges; Robbins and Ginader (58)). Diastolic pressure rises less (Köhler). The rise varies greatly with the individual. The effect lasts 30–40 minutes or even 70. Heart rate is usually reduced (pressor reflex) but in certain cases increased.

Veritol has little effect on blood sugar (Zipf). In susceptible patients such doses, or larger ones, produce other symptoms, such as pounding heart, sweating, and nausea, and may have some effect cerebrally, e.g. restlessness. Stumpf (49) presents some evidence that depth of anesthesia may be decreased.

SUPRIFINE, PARA-OXY-EPHEDRINE

Like ephedrine this substance has no effect on perfused vessels in the absence of epinephrine, but potentiates the latter's effect. It raises the blood pressure more rapidly than ephedrine and higher but shows less tachyphylaxis (Schaumann (61)). It has apparently a greater effect on the heart than on the vessels and is less toxic than ephedrine (Sturm and Stuckmann (60)). It produces, like ephedrine, no great change in the blood sugar level. A dose of 5 mgm., according to Oremus (32), increases the cardiac minute volume greatly without much, 5–10 mgm., rise in blood pressure and the effect may last for 45 minutes.

COBEFRINE. CORBASIL

This differs from the other ephedrine-like propanolamines in that the amine does not occur on the terminal carbon but on the middle one of the side-chain and is a direct isomer of epinephrine. It is about 1/2 (Schaumann) or 1/3 as potent as epinephrine (Tainter and Throndson (62)) but its effect lasts slightly longer and is prompt in onset. According to Tainter (46) it does not show tachyphylaxis and increases the effect of epinephrine moderately. It seems to have less effect on the vessels, but more effect on the heart (Schaumann 1931), though in Tainter's animal experiments the heart rate increased only 20 per cent. for an increase of blood pressure of 20–70 per cent.

CONCLUSIONS

1. One may therefore be permitted to draw certain conclusions. Ephedrine is of value in preventing a fall of blood pressure or in combating it if circulating epinephrine is available. If not, it should be

used with small doses of epinephrine subcutaneously, or in a great emergency intravenously. An endeavor should be made to estimate the dosage of both drugs so that blood pressure will not rise greatly, if at all, above normal levels. It is evident that synephrine might well be used in place of epinephrine as it does not increase the oxygen consumption of the heart so greatly and its action is potentiated by ephedrine, and this is substantiated by the work of Cranston and Bieter (63). Neosynephrine, though the rise of pressure it produces is somewhat longer, has less of the beneficial cardiac effect than synephrine. Further, there seems good reasons for the use of veritol in place of ephedrine, as its cardiac action is more favorable.

Finally, the differences between these substitutes is not so great that it would be wise for any anesthetist to learn to use one of the propanolamine group and one of the ethanolamine group wisely and skilfully rather than to experiment with a larger number. There are other members of both groups which have not been referred to at all, and which will doubtless be marketed and their claims pressed, but the anesthetist should not take them up without suspicion.

EPINEPHRINE SUBSTITUTES WITH LOCAL ANESTHETICS

2. It has recently been suggested that some of the epinephrine substitutes should be used in place of epinephrine with local anesthetic solutions. For this purpose it must be remembered that with the exception of arterienol they are all less effective than epinephrine. There does not seem any adequate reason for the employment of any of the ephedrine, propanolamine group particularly in view of the work of Tainter and Throndson (62), who have shown that the combination of cobefrine with procaine was definitely more toxic than of procaine with epinephrine. The combination of procaine with synephrine or neosynephrine would seem more reasonable and it may prove that the undesirable tachycardia might be lessened. This has been confirmed for neosynephrine (Tainter and Throndson).

POST PITUITARY EXTRACT

The vasoconstrictor actions of post pituitary extract were described by Oliver and Schäffer in 1895. The active principle was finally separated into two fractions by Kamm and Aldous. As is well known, the subcutaneous or intramuscular injection of 1 cc. of pituitary extract or of equivalent amounts of the pressor principle do not produce much rise in blood pressure in normal human beings; often there is no rise in systolic pressure and it rarely amounts to 15 mm. Hg. Diastolic pressure rises perhaps a little more but not often above 10 mm. The rise is slow in development and lasts 45 minutes (Schmidt (64)). The pulse rate is usually decreased. The regulating reflexes are adequate to prevent much pressure rise even though there is widespread vasocon-

striction in arterioles and capillaries. Unfortunately the coronary arteries are also constricted (Morawitz and Zahn (65)) and an endeavor to force the blood pressure up significantly usually leads to such a coronary constriction that the heart fails to cope with the strain imposed on it. A complete analysis of the effects of the pressor principle on the factors involved in the blood pressure changes such as has been made for epinephrine, etc., has not been carried out. Its usefulness is, however, greatly limited by the effect on the coronary arteries and even moderate doses may cause occasional severe cardiac embarrassment in man as it does, at times, in animals.

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EDITORIAL

NEED FOR ANESTHETISTS AND TRAINING FOR ANESTHETISTS IN THE PROGRAM OF PREPAREDNESS

One of the outstanding needs in our program of preparedness should undoubtedly be forehandedness. One of the pressing requirements of this program of preparedness is that we do not fail to learn lessons from the past experiences of the World War in relation to medical progress, and one which undoubtedly exists, the problem of anesthesia.

At the time of the World War, relatively little progress, as compared with the present, existed in anesthesia. The situation today, however, is quite different and, while it may never be possible to apply to the large group who must be cared for some of the more highly refined anesthetic procedures as the result of this development, we must not fail to have them in mind. We must not look upon the problem of the surgical and anesthetic management of the present-day soldier in the same light that we viewed the situation in 1917.

Nearly everyone would be willing to admit that the type of anesthesia which lends itself in terms of ease of availability and safety to army groups is ether. Nevertheless, no one with the soldiers' interest at heart can fail to appreciate that there should be available for those in whom it is especially needed some of the refinements which have occurred in the period between the World War and the present emergency. It is for this reason, I believe, that those who are in authority in medical preparedness should have in mind the question of special training in anesthesia of at least a limited number of men who wish to receive it, and thus make it applicable where it may very conceivably play a considerable part in saving the lives of soldiers when they might well otherwise be lost. No one who has had the opportunity to do surgery with the modern refinements of advanced anesthesia and anesthetists available could fail to appreciate the soundness of this statement.

I am certain that there are no organizations in this country possessing trained anesthetists that would not be willing to accept a reasonable number of medical officers who are interested in anesthesia. These groups, I am sure, would do everything in their power to assist in giving them a greater knowledge of some of these newer refinements in the shortest possible period of time.

Even if these medical officers could remain under the influence of trained anesthetists but a relatively short time, for example a few months, they could be taught some of the simplest and most valuable procedures, such as the administration of intravenous pentothal, the safe use of spinal anesthesia, the value of postoperative suction bronchoscopy, and the latest accepted treatment of shock with intravenous fluids, transfusions, and pain relieving drugs.

I doubt if there is any single trained anesthetist or groups possessing trained anesthetists who would be unwilling to accept men of this type for training, the benefit of which, it is my feeling, would be incalculable.

FRANK H. LAHEY, M.D.

SOUTHERN ASSOCIATION OF ANESTHETISTS

The Southern Association of Anesthetists is holding a joint meeting with the Section on Anesthesia of the Southern Medical Association in Louisville, Kentucky, November 12–15, 1940. The two-day program of this joint meeting will be as follows:

OFFICERS

Chairman—R. Douglas Sanders, M.D., Louisville, Kentucky.
Vice-Chairman—George S. Mechling, M.D., Oklahoma City, Oklahoma.
Secretary—Merrill C. Beck, M.D., New Orleans, Louisiana.
Hosts from the Jefferson County Medical Society—Dougal M. Dollar, M.D., Hiram S. Eggers, M.D., John W. Heim, M.D. and John A. Neblett, M.D.

Thursday, November 14—9 A.M.

1. Fields for Consultation Related to Anesthesia (Lantern Demonstration).

   By

   R. Douglas Sanders, M.D., Louisville, Kentucky.

2. Further Observations of the Allergy of Cyclopropane.

   By

   Russell F. Bonham, M.D., Houston, Texas. Discussion to be opened by C. W. Hoeflich, M.D., Houston, Texas.

3. The Clinical Use of Intravenous Anesthesia Alone and in Combination with Other Anesthetics: A Method of Anesthesia Eliminating the Hazards of Fire and Explosion (Lantern Demonstration).

   By

   Edward B. Tuohy, M.D., Rochester, Minnesota. Discussion to be opened by S. A. Peoples, M.D., Louisville, Kentucky.

4. The Treatment of Idiopathic Sciatica by Epidural Injection of Almond Oil and Novocaine (Motion Pictures).

   By

   Charles B. Odom, M.D. and M. C. Kolczun, M.D., New Orleans, Louisiana. Discussion to be opened by Michael E. De Bakey, M.D., New Orleans, Louisiana.

5. Outline for Teaching Anesthesia to Physicians of Small Communities.

   By

   Fred E. Woodson, M.D., Tulsa, Oklahoma. Discussion to be opened by Lester D. Norris, M.D., Fairmont, West Virginia.

6. Cyclopropane and Avertin Anesthesia at Western North Carolina Sanatorium.

By

Arthur C. Ambler, M.D., Asheville, North Carolina. Discussion to be opened by John W. Heim, Louisville, Kentucky.

Friday, November 15—9 A.M.

1. Title to be announced.

By

Hope Snider Ross, M.D., Enid, Oklahoma. Discussion to be opened by Joseph S. Parker, M.D., Louisville, Kentucky.

2. Anesthesia for Intracranial Surgery.

By

Donald H. Stubbs, M.D., Washington, D. C. Discussion to be opened by Fletcher G. King, M.D., Jacksonville, Florida.

3. The Importance and Management of Induction.

By

William A. Hamer, M.D., Charlotte, North Carolina. Discussion to be opened by Nora Dean, M.D., Louisville, Kentucky.

4. Intravenous Anesthesia Combined with Regional and Spinal Anesthesia (Lantern Demonstration).

By

William L. Sibley, M.D., Roanoke, Virginia. Discussion to be opened by Merrill C. Beck, M.D., New Orleans, Louisiana.

5. Anesthetics at Increased Pressure.

By

Chapman Reynolds, M.D., New Orleans, Louisiana. Discussion to be opened by P. K. Knoefel, M.D., Louisville, Kentucky.

Election of Officers.

An inquiry directed to Dr. Morris Fishbein of the American Medical Association just before going to press provides facts of interest to anesthesiologists. The Committee on Medical Preparedness of the American Medical Association is aware of the fact that there will be a need for men in the field of anesthesiology, and that when assignments are made, individuals best suited for them will be considered. Cooperation is being given to certifying boards and similar groups.

A subcommittee on anesthesiology of the Surgical Advisory Committee has been formed in the National Research Council, consisting of Drs. Ralph M. Waters, Madison, Wisconsin, Chairman; Lewis S. Booth, New York City; John S. Lundy, Rochester, Minnesota; E. A. Rovenstine, New York City, and Ralph M. Tovell, Hartford, Connecticut. This group is working on the standardization of anesthetic practices and similar functions. All are members of the American Society of Anesthetists, Inc.

ABSTRACTS

Editorial Comment: A fixed style of presentation for this department of ANESTHESIOLOGY has purposely not been defined. It is the wish of the Editorial Board to provide our readers with the type of abstract they desire. Correspondence is invited offering suggestions in regard to the length of abstracts, character of them, and source of them. The Board will appreciate the cooperation of the membership of the Society in submitting abstracts of outstanding articles to be considered for publication.

ROTHWELL, B. S.: *Vinethene: an inhalation anesthetic for rapid induction and quick recovery. Administered by open drop or in the gas machine for dental oral surgery.* Mil. Surgeon **86**: 452–456 (May) 1940.

"The purpose of this paper is to acquaint dentists of our success with Vinethene as an inhalation anesthetic agent for short operations. . . . The report is based on our experiences during the employment of Vinethene anesthesia in a large percentage of our operations during the past several months. In the past fifteen years in this clinic we have anesthetized 67,853 patients without a fatality. . . .

"In the Oral Division of St. Vincent's Charity Hospital, we have been using Vinethene both by the open drop method and by vaporizing it in the machine with nitrous oxide-oxygen. We attach a vaporizer to our McKesson or to our Heidbrink Simplex machine and obtain anesthesia with complete relaxation and without an excitement stage. The induction is as rapid as with any anesthetic gas and much more certain than with nitrous oxide. Unconsciousness usually occurs within 20–45 seconds after the first inhalation. We never have to anticipate a struggling stormy induction; even the most resistant patients sink into anesthesia quietly and promptly. At no time do we reduce the oxygen flow below the basal requirements of the patient.

"Therefore, we never see cyanosis and what is more important, none of our patients is subjected to anoxemia, not even for a short time. . . . Our patients recover promptly and completely. A vomiting patient is very rare. Patients are able to walk into an adjoining room as soon as the operation is completed. They do not sweat as they used to do when they struggled during excitement, so they are permitted to leave the clinic as soon as post-operative bleeding stops, even in cold weather. . . .

"Whenever a patient is to be rendered unconscious, a freely open airway is of first importance; first, last, and always. To guard against obstruction of the air-way from fluid, saliva or blood, an efficient suction device should be ready for immediate use. The ambulant clinic patients do not require premedication. Whenever possible, we prefer to administer anesthetics to a patient with an empty stomach. If the patient has eaten recently and the operation cannot be delayed we prefer Vinethene to any other anesthetic agent. We also prefer to operate upon the patient in the sitting position. We rarely use restraining straps."

J. C. M. C.

C. J. M. DAWKINS. *Convulsions Occurring Under Vinesthene Anesthesia.* Brit. Med. J. No. 4126, 163–164 (February 3), 1940.

The cause of convulsions which come on after anesthesia appears quite obscure. It is well known that vines-

thene deteriorates rapidly at any temperature, with the formation of aldehydes in considerable quantity. These aldehydes, on the addition of an acid or any hydrogen ion, will polarize and form resins which are definitely toxic to laboratory animals, causing convulsions. On the other hand, the mental symptoms would appear to indicate some form of cerebral damage, fortunately not of a permanent nature. So far as the author is aware no death under vinesthene anesthesia has yet been recorded, although in experimental animals an overdose has resulted in death from a condition resembling acute yellow atrophy. It is therefore recommended that anesthesia with vinesthene should not exceed an hour in duration. The author has, however, given it for three and a half hours without the occurrence of any untoward symptoms. Until a fatality occurs, which he hopes may never take place, it is unlikely that the pathology of vinesthene convulsions will be determined.

A. S.

COOK, W. B.: *Convulsions associated with nitrous oxide-ether anesthesia.* Northwest Med. **39**: 182–183 (May) 1940.

"This patient, a thin female of 29 years of age, was operated on at the Swedish Hospital on August 7, 1939. She had never had chorea or epilepsy.

"Nitrous oxide and ether anesthesia was administered by one of the regular anesthetists of the hospital. She had one-sixth of a grain of morphine and $\frac{1}{150}$ grain of atropine three quarters of an hour before operation. The cervix was coned out with a cervical electrode and a supravaginal hysterectomy for fibroid of the uterus was done. She was a very excitable and apprehensive person and had refused spinal anesthesia. She took the anesthetic poorly and there was more or less labored breathing at times.

"As the fascia was being closed, which was one hour and fifteen minutes from the beginning of the operation, she began to have twitching of the eyelids which rapidly spread to the muscles of the face and neck, and then to the arms and finally the entire body was in generalized convulsions. There was embarrassment of respiration and her pulse was weak. The convulsions actually lasted twelve minutes, but it seemed a lot longer than that to me.

"She was given oxygen without any improvement and then 15 cc. of calcium gluconate were given in the vein, thinking the condition might be related to tetany. This did not improve the situation. Five cc. of a five per cent. sodium solution were injected in the vein, and the convulsions rapidly subsided. The operation was completed and she was returned to her room. The convulsions did not recur. . . .

"Perhaps the causes of convulsions during general anesthesia are many and varied, and cannot be satisfactorily explained. It may suffice to know that such a condition, paradoxical as it may seem, may occur when you think the operation is almost completed. These convulsions occur late. They begin in the muscles around the eyes and face. The pupil is dilated, and instead of crowding the anesthetic, it should be removed entirely. Dr. Lundy recommends intravenous barbiturates, and in this case pentothal sodium was very helpful." Bibliography—4 references.

J. C. M. C.

MURPHY, FRANK J.: *Anesthesia and anoxemia in relation to the use of nitrous oxide.* Surg., Gynec. & Obst. **70**: 741–743 (Apr.) 1940.

Recent medical literature has brought forth a wealth of articles deal-

ing with the untoward effects following nitrous oxide anesthesia. Some hold that anoxemia or tissue anoxia is responsible; others maintain there is a toxic action of nitrous oxide itself.

There have been certain errors present in the clinical use of this drug, and these errors have come to be looked upon as truths, through long usage, particularly by those with little or no clinical experience. Unfortunately, some recognized authorities have set forth the dictum that anoxemia during the administration of nitrous oxide is a normal and harmless condition. Undoubtedly a large amount of damage has been done by administering nitrous oxide without sufficient oxygen. This is because wrong methods have been used, and it should be recognized that the damage is due to anoxemia.

It has been accepted by clinical anesthetists that nitrous oxide is neither toxic nor is it irritating to the tissue. There seems to be no evidence that patients have suffered ill effects when nitrous oxide has been given in the presence of sufficient oxygen. Nitrous oxide is a very weak anesthetic, and although it will produce sleep in most patients, it does not possess the property of producing muscular relaxation. Adjuncts which will produce the necessary relaxation fall under four headings: (1) premedication, (2) block, (3) addition of another general agent, and (4) asphyxia. Asphyxia is not a part of normal anesthesia.

It can not be too strongly stated that asphyxia should not be a normal accompaniment of nitrous oxide or any other anesthetic agent.

If by the term "surgical anesthesia" we mean a state in which muscular relaxation is present with adequate oxygen concentration, there is no such thing as surgical anesthesia produced by nitrous oxide and oxygen.

It is true that nitrous oxide properly given has very definite limitations as an anesthetic agent. If muscular relaxation is present with nitrous oxide, there must be more or less anoxemia. Therefore, any report of a laparotomy done under nitrous oxide anesthesia is also a report of a case of anoxemia.

If the limitations of nitrous oxide are understood and too much is not expected, it has a proper place in the armamentarium of the anesthetist.

If nitrous oxide is given with sufficient oxygen, it can be given for any length of time and to patients of any age.

The abandonment of secondary saturation technique, the promiscuous use of nitrous oxide by unskilled attendants and others in dental offices, and the "pushing" of nitrous oxide in surgical cases will soon prove that asphyxia, not anesthesia with nitrous oxide, is responsible for the untoward effects which recently have been receiving attention.

B. B. S.

BUREAU OF LEGAL MEDICINE AND LEGISLATION, AMERICAN MEDICAL ASSOCIATION: *Regulation of the sale of barbiturates by statute.* J. A. M. A. **114**: 2029–2036 (May 18) 1940.

"Twenty-seven states have enacted laws, as of May 1, 1940, regulating the sale of barbiturates. In all but one of these states, retail sales of such drugs to consumers may be made only on prescription. . . . The laws that have been enacted follow no well defined pattern with respect either to the framework of the law or to the drugs included. . . . In practically all of the states compounds, derivatives and preparations of the included drugs are covered. . . .

"In some of the laws reference will be found to a requirement imposing on pharmacists a duty to retain prescriptions for barbiturates or other included drugs in their files for a definite period of time. The absence of such a refer-

ence in other laws does not necessarily mean that there is no such requirement in those states, because there may be a general law imposing the requirement with respect to all prescriptions."

J. C. M. C.

EDITORIAL: *Barbital and its derivatives.* J. A. M. A. **114**: 2020 (May 18) 1940.

"Ever since urea was prepared synthetically by Wöhler in 1828 its derivatives have occupied an important place in medicine and in research. . . .

"In a report previously published in *The Journal* . . . it was shown that 'the evils of these drugs [the barbiturates] include habit formations, toxic cumulative action, their substitution for alcoholic beverages for drunken episodes, their use for successful as well as unsuccessful suicidal attempts, their improper use being a recognized causative factor in many motor accidents and their improper use being a recognized etiologic factor in some criminal assaults.' . . .

"Restrictions enforced by law have become increasingly necessary with the education of the public to the possibilities that lie in the ingestion of the malonylurea derivatives. . . . More rigid enforcement of restrictions on the prescribing of these potentially dangerous drugs has the whole-hearted approval of the Council and of *The Journal.*"

J. C. M. C.

HAMBOURGER, W. E.: *The promiscuous use of the barbiturates.* J. A. M. A. **114**: 2015–2019 (May 18) 1940.

"In a previous communication . . . a survey was made of coroners' records of suicidal deaths due to barbiturates. The present report deals with the involvement of these drugs in cases of poisoning received at hospitals during the decade 1928–1937. The data were obtained from fifteen hospitals in reply to a questionnaire. Additional data were added from the medical literature. . . . The statistics available for study represent more than one and one-fourth million hospital admissions for the decade 1928–1937. . . .

"One out of every 1,900 admissions was due to acute barbiturate intoxication. Barbiturates were responsible for one-seventh of the acute poisonings due to all drugs except alcohol and carbon monoxide. The fatality rate in the cases of acute barbiturate poisoning was 7.3 per cent. As each new barbiturate has been introduced clinically and has become publicized there has been a noticeable trend toward its use in poisoning cases. . . . Hypersusceptibility to therapeutic doses of a barbiturate was charged in thirteen cases admitted to ten of the hospitals, about one case for every 90,000 admissions. Addiction to barbiturates was the reason for admitting eighty-five patients out of the total of 1¼ millions admitted for all causes, about one barbiturate addict in every 15,000 admissions. Barbiturates accounted for more than 10 per cent. of all addiction cases, excluding chronic alcoholism, admitted to the thirteen hospitals. Two thirds of the barbiturate addicts who gave information claimed that they became familiar with the drug through a physician. Nearly a third of the addicts for whom the information was recorded developed craving when the barbiturate was withheld. None showed any serious withdrawal symptoms. . . . Despite the probable involvement of barbiturates in automobile accidents and criminal assaults, no data concerning such crimes are available." Bibliography —17 references.

J. C. M. C.

HADLER, A. J.: *Granulocytopenia following barbiturate therapy.* New England J. Med. **222**: 755–759 (May 2) 1940.

"Few cases of granulocytopenia due

to medication with the barbiturates have been reported. . . .

"M. L. M., a 30-year old, unmarried woman, was admitted to the Long Island Hospital April 28, 1939. Except for an occasional attack of asthmatic bronchitis, she had been well until 5 days previous to admission, when she developed a sore throat, a nonproductive cough, fever, malaise, hoarseness and vomiting.

"Physical examination showed reddening of the mucous membrane of the pharynx, palpable cervical nodes, hoarseness, and sibilant and sonorous rales throughout the chest. The white-cell count was 6500. The temperature, which was 102° F. on admission, fell promptly to 99 or 100. On May 5 the chest was clear and resonant, and the patient was asymptomatic save for a slight cough. . . .

"On May 4 for insomnia the patient was given 1½ gr. pentobarbital-sodium, but because of depression the next day it was discontinued. On May 5 one tablet of Allonal was given. Three hours later, after a shaking chill, the temperature was 102° F. The patient felt wretched, had a headache and could not sleep. On May 6 she was given 3 gr. Sodium Amytal and had a sound sleep without a 'hangover.' On May 7, 8 and 9 she received an Allonal tablet each night but did not sleep well. Because of pain over the left maxillary sinus, a history of sinusitis and a persistent fever of 99 to 100° F., x-ray films of the sinuses were taken on May 9; they showed thickened membranes in both antrums but no fluid level. The patient was discharged May 11 with a normal temperature.

"She felt well until May 19, when pain began in both submaxillary regions. Insomnia, headache, weakness and lassitude became marked. She took several aspirin tablets and two Allonal tablets on May 20. On May 21 she took more aspirin and another Allonal tablet. On May 22 at 1 a.m. her temperature was 101° F., and at 3:30 a.m. 103.4, after a shaking chill for 1 hour. She was readmitted to the hospital, where examination showed only tender submaxillary nodes. The hemoglobin was 95 per cent., the red-cell count 4,500,000 and the white-cell count 1050, with 4 per cent. neutrophils (band forms), 8 per cent. myelocytes, 80 per cent. lymphocytes, 4 per cent. monocytes and 4 per cent. eosinophils. A few hours later the white-cell count was 2250, with a similar differential count. . . . Therapy consisted only of 0.5 cc. of Reticulogen, a concentrated liver extract, administered intramuscularly once daily. The fever rapidly subsided. Coincident with an upper-respiratory infection there was a fall in the luekocyte and neutrophil counts after the original rise to normal, but recovery was spontaneous, since liver therapy had been discontinued when the counts first reached normal.

"The patient stated at this time that in 1936, following extraction of a tooth under novocain anesthesia, she had had local pain, adenopathy, sore throat, exhaustion and a fever of 101° F., and that she had been given some unidentified tablets. A low white-cell count, which she believed was 1200, was found. Other counts were taken and she was confined to a hospital, the records of which stated that her dentist had found a white-cell count of 3500, of which only 10 per cent. were polymorphonuclears (band forms). Later, blood studies at that hospital showed a hemoglobin of 81 per cent., a red-cell count of 4,620,000 and a white-cell count of 3000, with 16 per cent. neutrophils (5 per cent. band forms), 30 per cent. lymphocytes, 52 per cent. monocytes and 2 per cent. basophils. The temperature dropped rapidly to normal, and the patient was discharged with the diagnosis of mild agranulocytosis.

"On the second admission to the Long Island Hospital the patient complained of pain at the angle of the right jaw from a known infected and impacted wisdom tooth. An x-ray film showed no abscess formation. On June 7 she was given 10 cc. of 1 per cent. novocain subcutaneously to test for sensitivity. Since there was no change in the blood counts, on June 8 the tooth was extracted under novocain anesthesia. Following this there was a leukocytosis for about a week. The patient was discharged June 15.

"After discharge frequent blood-cell counts were taken. . . . On July 5, patch tests were done with acetylsalicylic acid, acetphenetidin, Allonal and barbital; all were negative. Tests were then begun in order to determine whether a drug had caused the granulocytopenia. Allonal * was suspected. On July 12, 13 and 14, doses of 5 gr. of acetylsalicylic acid were taken each day, with no resultant leukopenia or neutropenia. On July 17, 18 and 20, doses of 5 gr. of acetphenetidin were taken each day, with no subsequent leukopenia or neutropenia. On July 24, at bedtime, an Allonal tablet was taken. The next day both the white-cell count and the percentage of neutrophils had risen (7750, with 93 per cent. neutrophils). The patient felt marked lassitude, weakness and slight dizziness. The following night she took another Allonal tablet. The next day she was near prostration and had to remain in bed most of the day. The white-cell count was 4350, with 51 per cent. neutrophils. In 2 days the count had risen, and she felt fairly well again. Since Allonal had produced this effect and since acetphenetidin had produced no effect, the alurate component seemed responsible. Alurate was not available, but sodium alurate was obtained in 3½-gr. capsules (equivalent to approximately 3 gr. of alurate). On August 1 the patient was given a third of the contents of one of these capsules on retiring. The next day the white-cell count was 5800, with 70 per cent. neutrophils. The following night she took a similar quantity of sodium alurate, and the next day the white-cell was 2800, with 63 per cent. neutrophils. After the first dose of sodium alurate there was considerable lassitude and weakness; after the second dose the patient was prostrated. The white-cell count fell to 1800, with no neutrophils. . . . She remained weak and devoid of energy, the gums became sore, the submaxillary regions ached and the temperature gradually rose to 102° F. on August 7. That night she had cold chills and sweats. The right tonsillar region became sore, and two spots of exudate appeared there. There was anorexia, and severe headache.

On August 7 the patient received 1 cc. of Reticulogen intramuscularly. On August 8 the patient vomited, the cold chills continued and she was again hospitalized. She was given 1 cc. of Reticulogen intramuscularly, and later 10 cc. of Pentnucleotide intramuscularly in the buttock. Within 1 minute after the Pentnucleotide injection she noticed dryness of the throat; asthma set in with labored breathing and wheezing, and there was marked numbness down the inside of each arm and in the fourth and fifth fingers of each hand. The patient felt as though she were dying, the sensation beginning at the fingers and working upward. There was no substernal pain or constriction. One cubic centimeter of adrenalin gave prompt relief. Following this, two injections of 5 cc. of Pentnucleotide with 0.5 cc. of epinephrine and 1 cc. of Reticulogen were given daily. The Pentnucleotide produced mild transitory numbness of the fourth and fifth fingers. The white-cell

* Since January, 1939, Allonal has been composed of alurate (1 gr.) and of acetphenetedin (3 gr.).

counts steadily rose under this regime. The percentage of eosinophils rose to 30, suggesting an allergic reaction. During all stages of the illness, but especially during recovery, the patient showed many band forms and myelocytes, except during the extreme neutropenia. She always had a large number of platelets, many of them being very large. The red cells were essentially normal.

"The patient made an uneventful recovery and was discharged August 13. It had been hoped that the effect of Pentobarbital-Sodium could be determined by the test-dose method also, since it had a 'hangover' much like that caused by Allonal and sodium alurate, but it was deemed best not to risk the repeated production of granulocytopenia, and it was decided to avoid barbiturates in this case in the future.

"About 300 cases of granulocytopenia following the administration of amidopyrine and proprietary drugs containing it have been reported. In the latter group Allonal formerly belonged, but . . . since January, 1939, the formula has been changed from a combination of amidopyrine and alurate to one of acetphenetidin and alurate. No cases due to the 'new' Allonal, which this patient received, have been reported. . . .

"According to Jackson and Merrill . . . and Thompson, . . . 80 per cent. of the patients with agranulocytosis are women, and a remarkably large number of attacks of granulocytopenia occur at or about the time of the catamenia. . . .

"An interesting point for consideration is the similarity of structure of alurate (allylisopropylbarbituric acid or allylisopropylmalonyl urea) and Sedormid (allylisopropylacetyl carbamide or allylisopropylacetyl urea) and of their hematologic effects. . . . Apparently Sedormid, the structure of which is quite similar to that of alurate, can depress the leukocytes, particularly the granulocytes, as well as the platelets. . . .

"The reported case showed immature neutrophils during most of the granulocytopenic period. Whether the liver extract or Pentnucleotide speeded up the maturation process is uncertain, for at least twice, in 1936 and in June, 1939, she recovered spontaneously, but it is true that convalescence followed rapidly after treatment was initiated." Bibliography—23 references.

J. C. M. C.

ORNSTEIN, G. G.: *The relationship of muscle tonus and venous pressure under spinal anesthesia: A simple method for its control.* Current Researches in Anesth. & Analg. **19**: 157–162 (May–June) 1940.

"In two previous papers Ornstein, Licht and Herman have shown that by stimulating large surfaces of skeletal muscles with faradic current, the venous pressure could be raised. The work of the above investigators was stimulated by the writings of Yandell Henderson on his concepts of the mechanism of shock. . . .

"The above authors found that they could raise the venous pressure in a group of 42 adults in whom there were no symptoms of shock. . . . The pressures after muscle contraction rose from 1.5 cm. of water to 10 cm. of water. The average rise was 3.57 cm. of water pressure. It was also noted that within a few minutes after the discontinuation of the stimulation, the venous pressure dropped to the reading before stimulation and would rise again with further stimulation. The findings above noted fitted very well with the teachings of Henderson, and the authors then decided to apply this method of raising venous pressure in

the treatment of shock, either surgical or traumatic. . . .

"By employing over the summer months two medical students who were trained in applying the electrical therapy and in making venous pressure readings, all admission cases of traumatic injury were investigated for shock. Forty-seven cases were investigated and not one could be called in shock. . . . Our main difficulty, therefore, was in obtaining material for observation. We did find one case of traumatic shock. . . .

"A white male, 32 years of age, was in an automobile accident and sustained a fracture of the right tibia. When he was brought into the hospital he was in a condition of shock. The outstanding feature was the profound apathy. The skin was cold, clammy and gray in color. Breathing was characterized by periods of long sighing respiration. The venous pressure was down to 2 cm. of water and the blood pressure had also dropped. The pulse was weak. There was no diastolic pressure and the systolic was 80 mm. of mercury pressure. With faradic stimulation the venous pressure rose to 10 cm. of water and the arterial blood pressure rose to a systolic of 95 mm. of mercury and a diastolic of 60 mm. of mercury. The sensorium cleared and the patient after 45 minutes was completely out of the state of shock. One cannot draw any conclusions from just one case. . . .

"The close resemblance of the syndrome which follows the injection of anesthetic into the spinal canal, to the condition we term shock has been of extreme interest to my associates and myself because of the possibility of applying this electrical stimulation of the skeletal muscle for the control of those disagreeable symptoms following spinal anesthesia which occasionally can be responsible for the loss of a life. . . .

"My associates and I thought we would not have the same difficulty in obtaining material to test the effect of electrical stimulation of skeletal muscles in the control of venous pressure in spinal anesthesia that we had in obtaining cases of shock. . . . We have little material on which to base a report. Altogether, we had nine cases. The first case availed us little. The patient had a severe case of infantile paralysis. There was little muscle to stimulate and there were no changes in venous pressure. The venous pressure did not recede from the pre-operative figure of 7.4 cm. of water. In two succeeding cases there was a definite rise of the venous pressure with muscle stimulation.

"In one male, white, 55 years of age, there was an injection of 150 mg. of neocaine into the spinal canal between the second and third lumbar vertebrae. The venous pressure dropped from 7 cm. of water to 3 cm. of water following injection of the anesthetic. With muscle stimulation it rose to 15 cm. of water. There was no change in the arterial pressure, which remained at 120/70. In the other case (one female, white, 34 years of age), following an injection of 120 mg. of neocaine into the spinal canal between the second and third lumbar vertebrae, the venous pressure dropped from 5 cm. to 3 cm. of water. With faradic stimulation the venous pressure rose to 12 cm. of water. . . .

"Six cases were observed at the Bellevue Hospital. . . . In the *first case*, after spinal anesthesia, the patient developed a severe drop in blood pressure followed by circulatory depression (shock) with blood pressure and venous pressure readings at zero and a rapid, weak, thready pulse. During some of the time while the patient steadily progressed to this condition, the stimulator was being used. It effected no change. Oxygen and ephedrine were finally needed to relieve

syncope. In the *second case,* the stimulator was applied during the time venous pressure was decreasing. During ten minutes of stimulation no further rise or fall in venous pressure was observed. There was a further drop after stimulation was stopped. In the *third case,* spinal anesthesia caused venous pressure to fall from 6 to 2.5. There was no change thereafter during several ten-minute periods when the stimulator was in use." "In the other three cases Rovenstine obtained no effect on the venous pressure by faradic stimulation. . . .

"Why the faradic stimulation had raised the venous pressure in three of the six cases at Bellevue and failed in the other three I cannot explain. Nor do I wish to draw any conclusions from the above few cases except to hope that some of you anesthetists will be sufficiently interested to investigate this procedure more thoroughly than my group has been able to do. The method holds forth the possibility of aid in circulatory changes due to venous failure and should be given a better opportunity to determine its value than my group was able to furnish." Bibliography—5 references.

J. C. M. C.

CHAIKOFF, J. S.: *Efficacy of the combination of ephedrine and pitressin as preanesthetic medication in the control of blood pressure during spinal anesthesia.* Current Researches in Anesth. & Analg. **19**: 121–131 (May–June) 1940.

"Louis H. Maxson in his book 'Spinal Anesthesia' states that 'the fall in blood pressure is the most important and serious of the indirect results of spinal anesthesia.' Even a cursory examination of the literature on the subject reveals the worry and agitation that our pioneers experienced in the early days of spinal anesthesia. I believe that one does not exaggerate in stating that the repeated abandonment of this type of anesthesia as too dangerous was due to lack of control of blood pressure. . . . To state the problem briefly, Samson Wright maintains that blood pressure depends on cardiac output and the peripheral resistance offered by the arterioles and capillaries. Maxson quotes Roeder more explicitly: 'Blood pressure is maintained by four factors: (1) Myocardial tone, and (2) Arterial tone, on the one hand, acting against (3) Capillary resistance, and acting upon (4) An ample volume of blood furnished in the heart. . . .

"The vasomotor control of the entire body, and an important part of the mechanisms controlling cardiac action and respiration, are concentrated between the first thoracic and third lumbar segments of the spine. When the anesthetic drug is injected into the subarachnoid space and as the drug extends upward, more and more white rami communicantes are paralyzed. Consequently a progressively larger area of the body loses its vasomotor control and the peripheral resistance is progressively decreased, leading to a profound fall in blood pressure. At the same time, more and more intercostal nerves are paralyzed and the breathing becomes shallow and inefficient, thus interfering with the venous return to the heart. This interference is further augmented by the loss of intra-abdominal pressure, being due to both the incision and the relaxation of the abdominal muscles. Should the drug reach as high as third and fourth thoracic segments, the cardiac acceleratory nerves are paralyzed, leaving the vagus unopposed, the heart rate then dropping to 40–50 per minute. An unopposed vagus may also constrict the coronary circulation, seriously interfering with the oxygen supply to the heart muscle, this leading to partial and possibly complete heart failure. From the physiological standpoint, however, the nervous con-

trol of the coronary circulation is not at the present considered to be of great importance.

"Thus we have four factors leading to a drop in blood pressure. (1) Loss of peripheral resistance. (2) Slowing of the rate of contraction of the heart. (3) Inefficient venous return due to shallow respiration and loss of intra-abdominal pressure, and (4) Possibility of coronary constriction by the vagus.

"To overcome this many methods and many drugs have been employed. The Trendelenburg position was stressed by many early investigators, postulating anemia of the vital centers. Inhalations of aromatic spirits of ammonia were found by Babcock to raise the blood pressure 6–12 mm., and Maxson considered its administration to be of good psychic value. A. I. Willinsky exhorted his patients to take a deep breath. . . . An intravenous injection of saline solution was found useful by Babcock. Jonnesco and Pitkin injected strychnine intrathecally and after many years found it to be useless. Labat tried caffeine without success. All investigators used adrenalin as a last resort. . . .

"As far back as 1895, Oliver and Schaefer showed that the extract of the posterior lobe of the pituitary gland exerted a vasopressor effect if injected into animals, and that the effect was more lasting than adrenalin. . . . The first clinical report on the use of ephedrine in spinal anesthesia was presented before the American Society of Therapeutics in 1926 by Rudolf and Graham of the University of Toronto. After a thorough investigation of its properties in the pharmacological laboratories, Dr. J. D. Graham set about looking for cases of asthma and hypotension, and at the suggestion of Dr. A. I. Willinsky decided to test this new drug as to its effect on low pressure during spinal anesthesia. . . . Chen and Meek in 1926 have shown that large doses of ephedrine lower, not raise, the blood pressure and depress the automatic and conductive system of the heart; also that subsequent small doses of ephedrine are not as effective in raising blood pressures as the first, both in time and height. . . .

"In 1931, Melville and Stehle published a report on a series of experiments showing that the addition of ephedrine leads to augmentation of the pressor response to small doses of pituitary extract; that it will abolish the depressor action of large doses; that it will abolish the diminution of cardiac output after large doses. He [Melville] explained the above results by the fact that ephedrine prevents the constriction of the coronaries by pituitrin. His conclusion was that they exert a symbiotic action on the cardiovascular system.

"The present report is based on a series of 119 cases with three distinct techniques.

"Technique I.—Ephedrine gr. i (75 mg.) is administered intramuscularly about 8–10 minutes before the spinal puncture.

"Technique II.—A mixture of ephedrine ½ gr. (40 mgm.) and pitressin ½ c.c. is administered 8–10 minutes before the spinal puncture.

"Technique III.—As in technique II, but the dose is repeated just before the incision, provided the blood pressure shows a tendency to drop while the patient is being draped.

"The comparative efficacy of these techniques was judged on the basis of a drop in blood pressure within an hour after the puncture, sufficient to justify the use of vasopressor drugs. As a rule, if the pressure dropped to less than 80 or 90 systolic, drugs were administered. . . . Administration of the spinal anesthetic was, with a few exceptions, in accordance with the Howard Jones technique. . . . The drugs

used as a rule are nupercaine (Ciba) 1:1500 and procaine 10 per cent. In this series over 96 per cent. of cases were given nupercaine. . . . When ephedrine alone was used 37.7 per cent. of cases failed to maintain blood pressure. When the combination of ephedrine and pitressin was used 8–10 minutes before spinal puncture, 22.2 per cent. failed; and when used twice, i.e., repeated just before the incision, only 7.8 per cent. failed. These figures speak for themselves. The combined groups give 14.8 per cent. failures. . . .

". . . we made several other observations. Foremost among these was the widening out of the pulse pressure. . . . It is logical to suppose that an intravenous injection of saline or saline and glucose will help stabilize the volume of blood disturbed by the incision and trauma. . . . From the standpoint of the surgeon, Dr. A. I. Willinsky volunteered the observation that with pitressin the gastro-intestinal tract is still further contracted and is entirely kept out of the field of operation. Should we happen to give an overdose of the combination we find no alarming results. The systolic pressure climbs up gradually to about 40 mm. above the preoperative reading and gradually returns to normal. . . . Readings were taken about one or one and one-half hours after the patient was returned to his bed and almost all of the readings showed no marked drop, but either a good maintenance or a return to normal pressures. In hypertensive cases we administered the combination only once (Technique II), with no untoward results. . . . The ages of the patients in this series included both extremes, 14 years being the youngest and 81 + the oldest. . . .

"Finally we would plead with surgeons who use pitressin in repeated doses to prevent or cure postoperative distention, to use the drug only in combination with ephedrine." Bibliography—26 references.

J. C. M. C.

BEUTNER, R.: *Studies in the detoxification of procaine.* Current Researches in Anesth. & Analg. **19**: 132–140 (May–June) 1940.

"Procaine hydrochloride is generally considered a safe local anesthetic, since in many thousand of instances it is administered without the slightest disturbance. Unexpectedly and, perhaps surprisingly, accidents will happen at times. We are thus reminded that it is a poison which may elicit violent convulsions or collapse, if by chance a high concentration reaches the cerebral centers. Like all local anesthetics procaine is kept from resorption in the general circulation by the addition of a vasoconstrictor like adrenalin (epinephrine), but this again is a violent poison. Efforts have therefore been made in my laboratory . . . to find less dangerous detoxifying agents. . . .

"The aim of the first line of work undertaken was to find a more penetrating procaine preparation. It is known that the addition of sodium bicarbonate renders procaine hydrochloride more penetrating. I found that procaine base can be dissolved by means of carbon dioxide directly, thus avoiding completely the use of a hydrochloride. . . .

"Solutions of procaine, prepared by this method, were studied pharmacologically according to the method described by G. P. Miley and this writer —for gauging the convulsive power of local anesthetics. The essence of this method is to observe the incidence of convulsions following the injection of a procaine preparation. . . .

"With larger procaine doses, the solution containing carbon dioxide was somewhat more convulsant than the hy-

drochloride but the difference was, after all, not very considerable. . . .

"It seems, therefore, that when injected intramuscularly, then allowed slowly to pass into the blood stream, procaine is liberated to nearly the same extent whether combined with hydrochloric acid or with carbon dioxide. Quite a different result was obtained, however, when the local action of these two procaine solutions was studied. As a strictly local action, the anesthetic effect on the cornea of a rabbit was tested. It was found to be more extensive for procaine dissolved by carbon dioxide than for procaine hydrochloride. . . .

"G. P. Miley and this writer . . . have shown that calcium chloride allays procaine convulsions. In order to demonstrate this point, [a] . . . statistical method was used. The method consists in injecting a large number of guinea pigs with the same dose of procaine with or without various drugs. The incidence of convulsions is noted. Guinea pigs were selected for these tests since they survive these convulsions except after high doses, while rabbits almost invariably die after procaine convulsions. . . .

"As examples, the following details of the observations may be quoted: 100 mg./kg. of procaine hydrochloride gave convulsions in 84.2 per cent. of the injected guinea pigs (204 being injected, observations by Dr. Wastl; Beutner and Miley quoted 86.7 per cent. in 139 injections). When 25 mg./kg. of calcium chloride were injected, the incidence of the convulsions was only 50.3 per cent. (36 injections, observations by Dr. Wastl). When 50 mg. were added 25 per cent. of the animals had convulsions; when 100 mg. were added 14.2 per cent. of the animals had convulsions (observations by Dr. Wastl, 36 injections; Beutner and Miley quoted 14.6 per cent. in 48). When 200 mg. were added no convulsions were seen at all. . . .

"Beutner and Miley . . . had alalready found that this anticonvulsive action of calcium chloride is a strictly local one; it works in the described manner only if the local anesthetic and calcium chloride are mixed and injected simultaneously. . . .

"The nature of this local anticonvulsive effect of calcium chloride can be understood if we add both magnesium chloride and calcium chloride to procaine hydrochloride. One might assume that such a salt combination would be more effective than calcium chloride alone, especially since magnesium chloride is known for its depressing effect on the central nervous system. However, this assumption proves to be incorrect. Magnesium chloride counteracts the anticonvulsive effect of calcium chloride. . . .

"From all the observations described, it is evident that calcium chloride detoxifies procaine hydrochloride by rendering tissue membranes more impermeable, in this fashion, preventing a rapid diffusion of the poison and protecting the cerebral centers from convulsions. . . .

"In order to be certain of the value and correct functioning of the statistical method used with calcium chloride the anticonvulsive effect of epinephrine was studied by this method (experiments by H. Wastl). Indeed, it was found that a slight addition of epinephrine very markedly decreases the incidence of procaine convulsions. . . . Strange though it may seem, ephedrine, a well known vasoconstrictor, shows no such detoxification. . . .

"In a very thorough investigation, W. J. R. Camp showed that potassium chloride, or other potassium salts, injected in large doses, have an epinephrine-like action. One should expect, therefore, that potassium salts may also relieve procaine convulsions. Ex-

periments have shown that this is the case, although the effect is not very large. . . .

"A study of the calcium salts of organic acids seemed advisable because of the considerable irritation produced by intramuscular injection of calcium chloride. . . . In our experiments the irritant action of calcium chloride was distinctly noticeable. . . . It must be added, however, that such an inefficiency of calcium gluconate is observed only when it is added to and injected simultaneously with the local anesthetic. If calcium gluconate is injected separately it is not entirely inactive. . . .

"In an attempt to explain the slight anticonvulsive action of calcium gluconate on simultaneous injection it seemed reasonable to assume that the calcium content *per se* was not so important as perhaps the calcium ion content. . . . The conclusion is that calcium gluconate does not contain any calcium ions at all; obviously this is the reason why it completely fails to relieve procaine convulsions. . . .

"This absence of electric conductivity, or of ionization, of calcium gluconate is quite a rare and peculiar property. So far as known today no other calcium salt is completely non-ionized. The other organic calcium salts investigated so far are all ionized completely or nearly so. . . .

"Another extensive experimetal series was carried out, using butyn sulphate in the place of procaine as a local anesthetic. As is well known, butyn is a higher homologue of procaine, differing from it in possessing a butyl group in the place of the ethyl group of procaine and a propanol group in place of the ethanol. Accordingly butyn is much more toxic. It is convulsant in doses as low as 20 mg./kg.: 18 animals were injected; all had convulsions, yet survived. With doses as high as 50 mg. or more, all of the injected animals died, since their convulsions were extremely violent. Nevertheless calcium salts were seen to inhibit these violent butyn convulsions quite efficiently. . . .

"All the anticonvulsive agents mentioned so far act by rendering the tissue membranes or the brain centers less permeable. All these have no effect if injected separately or later. They are inactive after procaine has reached the brain. It is known that barbiturates and other centrally depressing drugs also check procaine convulsions. (Tatum and others.) However, this action, in contrast to that of calcium salts appears only if the barbiturate is administered 15 to 30 minutes before the local anesthetic. It was found that if pentobarbital or phenobarbital is mixed with procaine solutions and injected simultaneously, the incidence of expected convulsions is even higher than if procaine is given alone. . . . If the same amounts of these barbitals were injected half an hour earlier than the procaine, no convulsions appeared at all. . . .

"Another depressing drug was tested, calcium bromide. This was found to act exactly like calcium chloride. The same anticonvulsive action was seen which undoubtedly is due to its calcium content, while the bromine, in spite of depressing effect, plays no part.

"These observations show that the barbiturate or bromide has no effect on cell permeability. Its central depressing action is considerably slower than the central stimulating, or convulsant, action of the local anesthetics." Bibliography—5 references.

J. C. M. C.

E. FRIAS AND F. FERNANDEZ. *Postoperative Plate-like Atelectasis.* Current Researches in Anesth. & Analg. 19: 98–101 (March–April), 1940.

"Aside from infection of the bronchi, aside from massive and lobar

atelectasis and infarction, which are not included in this discussion, we meet with complications of a definite pneumonia type. Among our patients this is the most frequent form of post-operative pulmonary complication. It is in this type of complication that partial atelectasis is of great etiological importance. When we speak of partial atelectasis we refer to plate-like atelectasis. In this study we desire to report the clinical and radiological characteristics of this postoperative complication. . . .

"The signs [of plate-like atelectasis] develop mostly in the base of the lung, hence the greatest frequency of plate-like atelectasis in this situation. In any portion of the base of the lung, extending horizontally and being near the costal region, where the finer bronchi end, there is a respiratory and circulatory disturbance and in this bronchiolar system some mucus accumulates. After a certain time we have blocking of that part of the bronchial system and the air in the alveoli is re-absorbed. Soon that area of the lung does not exchange air and tends to collapse. This is possibly only in one direction — lengthwise — because transversely the parenchyma is supported by the hilus, mediastinum, and by the negative intrathoracic pressure that keeps the lung contiguous to the thoracic wall. . . .

"In massive and lobar atelectasis the collapse or retraction is so great that it even acts on the mediastinum and costal wall, giving a characteristic radiological picture. In plate-like atelectasis the retraction is not sufficient to displace the mediastinum and ribs, these parts remaining in situ. Thus Fleischner explains the formation of plate-like atelectasis and that is the reason he also calls them 'directed lung collapse.' . . .

"One sign is always present in plate-like atelectasis, elevation and reduced movement of the diaphragm. In the majority of our cases, not only has atelectasis been present, but we have also found a pneumo-peritoneum which would seem to be of some importance as an etiological factor.

"It is possible to mistake plate-like atelectasis for incisuritis, it is less likely to confuse the atelectasis with pleural adhesions. But careful radiological study will clarify the diagnosis. . . .

"Plate-like atelectasis is generally an early complication and does not affect the general condition of the patient. The clinical picture is that of one recently operated, with some cough, dyspnea of the expiratory type, slight increase in temperature and moderate tachycardia. In almost all cases there is a seromucoid or mucoid expectoration. This condition lasts three or four days and gradually subsides. In severe cases there is thoracic pain, higher temperature and great dyspnea, cough with mucopurulent expectoration, all of which produces a marked effect on the general condition of the patient. These symptoms indicate that infection is complicating a pure atelectasic process. . . .

"In cases of moderate severity there is slight dullness over the respective bases, diminished breath sounds, bronchial breathing and pectoriloquy. In some cases bronchial râles are heard.

"In more severe cases there is dullness, râles, bronchial breathing, bronchophony and pectoriloquy. This clinical picture lasts for five or six days and then gradually subsides. The last signs to disappear are the râles and the aphonic pectoriloquy.

"The X-ray findings persist for some time and in all of our cases, although there were no clinical signs at the time, X-ray examination revealed the persistence of the atelectasic shadow for fifteen or even thirty days after. . . .

"We have followed the clinical post-operative course of 566 cases, in 17 of which we found plate-like atelactasis

by X-ray examination. Apart from these cases of atelectasis we found a pleuropneumonic process in two others and in still another a mediastinal diaphragmatic pleural process. All cases with pulmonary or clinical signs were subjected to X-ray, as well as a series of over fifty operated patients who had no lung signs. Among the latter we discovered a case of plate-like atelectasis after a cholecystectomy.

"In over 95 per cent. of our cases ether was used as the anesthetic. It was administered with Ombredanne's apparatus or as nitrous oxid-oxygen-ether in open circuit. Only rarely was local or spinal anesthesia employed.

"Of the 17 cases of plate-like atelectasis, 16 followed laparotomy, 8 of which were supra-umbilical and 8 were infra-umbilical. After only one extra-abdominal operation (abscess of the liver) did this complication occur and in this instance the transthoracic method was used with novocain as a local anesthetic."

MOUSEL, L. H.: *Bronchoscopic treatment of postoperative atelectasis.* Proc. Staff Meet. Mayo Clin. **15**: 261–264 (Apr. 24) 1940.

"Atelectasis is perhaps one of the most frequent postoperative pulmonary complications. It is true that the majority of pulmonary complications, as reported in the literature, are cases with bronchopneumonia; however, it is my belief that most cases reported as postoperative bronchopneumonia are actually cases of postoperative atelectasis. Several hypotheses have been advanced as to the etiologic factors involved in producing atelectasis. . . .

"It is my opinion that most postoperative atelectasis is caused by an actual plugging of a bronchus by tenacious mucous secretion which has collected in the tracheobronchial tree during anesthesia, by tenacious mucopurulent material which was present preoperatively, or by mucus, blood or vomitus which has been aspirated into the trachea either during or immediately following anesthesia. The onset of actual atelectasis is probably gradual. The bronchus becomes plugged, causing a preliminary emphysema. If the patient is unable to remove the plug by coughing or change of position, the air in the involved region will be slowly absorbed in the blood stream until collapse is complete. Usually the patient will complain of dyspnea which is frequently out of proportion to the degree of pulmonary involvement. There is usually a sense of discomfort on the side of involvement in association with the atelectasis; the pulse becomes rapid, there is a sudden rise of temperature and cyanosis becomes apparent, the degree of cyanosis depending on the amount of lung tissue involved.

"In massive atelectasis the heart and mediastinal structures are shifted toward the side involved; breath sounds become diminished or absent, and the respiratory excursion on the affected side becomes diminished. The success of bronchoscopic aspiration depends on early recognition of the condition and early treatment, for if the condition is allowed to exist for any length of time mucopurulent material collects in the bronchus distal to the point of obstruction and with secondary infection a true pneumonitis or pulmonary suppuration develops.

"The usual procedure for the treatment of postoperative atelectasis has been the frequent changing of the patient's position in bed in order to encourage gravity drainage, the inhalation of 5 or 10 per cent. carbon dioxide with oxygen to promote deep respiration, and encouraging the patient to cough. While these measures seem to be of benefit in some cases, in many

other cases the response is not satisfactory.

"I wish to present three cases of atelectasis which were successfully treated by bronchoscopic aspiration.

REPORT OF CASES

"*Case 1.*—A man, sixty years of age, was submitted to cholecystectomy under ethylene, oxygen and ether anesthesia. Anesthesia was uneventful except for a fall of blood pressure from 160 mm. of mercury systolic at the beginning of operation to 95 mm. of mercury systolic at the termination of operation. Twelve hours after operation, cyanosis developed. There were definite signs of atelectasis in the left lower lobe. Roentgenologic examination of the chest at that time confirmed the diagnosis. . . . The left main bronchus was aspirated of a large amount of bile-stained material. Within a few minutes following aspiration breath sounds were coming through. A roentgenogram of the chest taken twenty minutes following aspiration showed that atelectasis had disappeared. . . .

"*Case 2.*—There was nothing unusual in the clinical history of a woman, twenty-six years of age, with the exception of chronic upper respiratory infection. Appendectomy and cauterization of the cervix were done under nitrous oxide-oxygen and ether anesthesia. Anesthesia was uneventful. Twelve hours after operation the patient began to cough. Some musical inspiratory râles were heard over the chest, but the chest was resonant throughout. Twenty-four hours after operation the patient complained of 'lower chest pain' referred through to the back. At this time there were distant breath sounds on the right and the entire right side of the chest was dull to percussion. Some bronchial breathing could be heard over the upper third of the right lung. The temperature at this time was 98.8° F. (37° C.). The patient became cyanotic. Roentgenologic examination of the chest showed massive atelectasis of the right lung. . . . The patient was turned frequently from side to side, 5 per cent. carbon dioxide in oxygen was administered at hourly intervals, and she was encouraged to cough. The cyanosis persisted, and on the second postoperative day her temperature was 101.4° F. (38.5° C.); massive atelectasis was still present. Bronchoscopic examination showed an inflammatory reaction around the right middle and lower lobe bronchi. . . . Gentle dilation was carried out. Following dilatation of the edematous tissue a small, tenacious mucous plug could be seen. This mucus was removed by aspiration. Four hours following bronchoscopy there was no dullness over the right side of the chest. . . . Fourteen hours following bronchoscopy there was evidence of consolidation in the right lower lobe; however, this condition rapidly cleared up, and on the fifth postoperative day the chest was clear and the body temperature had gone back to normal. Convalescence was uneventful. It was interesting to note the ball-valve action of the mucous plug which was found distal to the edematous mucous membrane in the right lower lobe bronchus; for, following aspiration, the atelectasis apparently cleared up completely, but it was found to be present again fourteen hours after aspiration. I assume that the edema continued to obstruct the bronchus following aspiration and atelectasis once more developed in the right lower lobe. However, the irritating mucous plug had been removed so that the edema soon subsided and the lobe once more became filled with air.

"*Case 3.*—An obese woman, thirty-one years of age, had a slight cough on admission to the hospital. Cholecystectomy was done under nitrous oxide-oxygen, carbon dioxide and ether an-

esthesia. Anesthesia was uneventful. Twenty-four hours after operation the patient had a chill which lasted five minutes. She complained of pain in the right lower portion of her chest. There were decreased breath sounds and decreased resonance over the right base. Her temperature was 100.6° F. (38° C.). Roentgenologic examination showed atelectasis in the right lower lobe. . . . The patient was submitted to bronchoscopy immediately. The right lower lobe bronchus was completely plugged with very tenacious glistening white mucus. The right middle lobe bronchus contained some mucus. The membrane of the entire right main bronchus appeared inflamed. There was no visible edema. The mucus was aspirated and the patient was sent back to her room. A half hour after aspiration the patient stated that she felt much better, and there were no physical signs of atelectasis at this time. Roentgenologic examination the following morning showed the right lower lobe completely aerated. . . . The patient continued to have a productive cough for several days; otherwise convalescence was uneventful." Bibliography—10 references.

J. C. M. C.

GRIFFITH, H. R.: *The prevention and treatment of complications during cyclopropane anesthesia.* Current Researches in Anesth. & Analg. **19**: 141–144 (May–June) 1940.

"The most important consideration in the use of cyclopropane, as with all other general anesthetic agents, is the maintenance of a free airway. . . .

"Of our series of 5,000 cases, endotracheal technique has been used 1,567 times. This is our routine method for all tonsillectomies, even with small children, and for all head and neck and certain abdominal cases. . . . I cannot urge too strongly upon anesthetists, the advisability of familiarizing themselves with the introduction of endotracheal tubes. I am sure that lives have been lost needlessly because anesthetists have been unable to introduce a tube quickly in an emergency. . . .

"Another matter of prime importance in the prevention of complications is the adequate use of suction in order to remove blood, mucus or other obstructing materials from the pharynx and the trachea. . . . Patients with full stomachs are dangerous anesthetic hazards, whether one is to administer cyclopropane or another agent.

"In order to keep out of trouble with cyclopropane, one should study all the factors of any particular case and decide on the method which will give the greatest safety under any circumstances which may arise. . . .

"Another doctrine which Dr. Leech and I have been preaching in regard to cyclopropane, is that it should be given unmixed with ether or other anesthetic agents. Whether this is as important as we believe only time will tell, but we feel that the unsatisfactory results which some have reported during or following cyclopropane anesthesia are not due to the cyclopropane, but to the ether which is so frequently mixed with it. We have never, for the last three years, found it necessary to add ether to cyclopropane, and this is in spite of the fact that 586 anesthesias have been for operations in the upper abdomen. . . .

"However, in spite of all our precautions, complications sometimes do occur, and in my opinion the most important ones to be considered are respiratory depression, pulmonary edema, atelectasis, cardiac arrhythmia and postoperative shock. . . .

"The toxic effects of cyclopropane are practically always manifested by respiratory arrest before there is any effect on the heart, so one has time to establish artificial respiration while the circulation is still good. Oxygen should be administered promptly,

either by manual pressure on the bag and mask or through an endotracheal tube which can be introduced. . . . However, in the average patient, cyclopropane is neither a respiratory irritant nor a depressant, and one should not have difficulty with the breathing more frequently than in perhaps one case in fifty. . . .

"I have reported elsewhere two cases of acute edema of the lungs which we observed in patients during and after cyclopropane anesthesia. These were treated by endotracheal suction and the administration of oxygen without serious after effects. . . .

"There have been several reports of fatal collapse of the lungs following the use of cyclopropane anesthesia. . . . In all our five thousand cases of cyclopropane anesthesia, we have had no single case of serious collapse, and the incidence of milder forms of partial atelectasis is less than it used to be following ether, ethylene or nitrous oxide and ether. I believe that the factors which prevent atelectasis are: (1) Open airways during and after anesthesia. (2) Nonirritating anesthetic. (3) Adequate use of pharyngeal and tracheal suction after anesthesia. . . .

"Many anesthetists have been concerned about the use of cyclopropane on account of reports regarding cardiac irregularities occurring during the course of anesthesia. I have frequently observed this phenomenon and I do not understand the reason for it, but I do know that I have never seen any permanent effect on the patient, and I do not believe that it has any particular clinical significance. . . . Clinical experience leads me to the firm belief that cyclopropane is the safest anesthetic agent which we have available at present for patients with serious heart disease who require a major surgical operation. We have repeatedly used it for our very poorest cardiac risks, including patients with advanced myocarditis and decompensation, and we have had no unsatisfactory results. . . .

"Patients who have had cyclopropane anesthesia for any extensive abdominal operation, or for some other type of operation in which there has been severe blood loss, sometimes show evidence of more or less serious shock, and the anesthetist may be called upon to assist in supportive treatment. I have found that coramine in doses of at least 5 cc. hypodermatically is a useful stimulant and that oxygen is of value, but that our principal reliance should be upon intravenous injections of glucose saline, or early blood transfusions."

J. C. M. C.

BUREAU OF LEGAL MEDICINE AND LEGISLATION, MEDICOLEGAL ABSTRACTS: *Workmen's compensation acts: death from pneumonia following reduction under ether of fracture of pelvis.* J. A. M. A. **114**: 2055 (May 18) 1940.

"In the course of his employment as a miner, on Feb. 22, 1938, the workman was caught under a fall of slate. After first aid treatment, the workman was taken in a closed automobile some 52 miles to a hospital. Physicians there found a 'fracture of the left ilium extending down to the acetabulum' and determined that it would be necessary to reduce the fracture under ether, which was done two days later. February 27 pneumonia developed and the workman died March 4. The industrial commission of Virginia, in proceedings that were instituted under the workmen's compensation act of that state, found that pneumonia, the immediate cause of death, had not resulted naturally and unavoidably from the industrial accident and denied the workman's widow and children compensation. The claimants then appealed to the Supreme Court of Appeals of Virginia. . . .

"The industrial commission found that the administration of ether to the workman had had nothing whatever to do with the pneumonia that subsequently developed, that the germ had already been present in the workman and that the pneumonia had developed coincidentally during the period of hospitalization for the fracture. The commission concluded, therefore, that the industrial accident had not been a producing cause of death.

"The Supreme Court of Appeals of Virginia, however, disagreed with the conclusions of the industrial commission. An accident to an employee which sets in motion his undeveloped and dangerous physical condition with mortal consequences is properly classable as the proximate cause of the fatality. Causal connection is established when it is shown that an employee has received a compensable injury which materially aggravates or accelerates a preexisting latent disease which becomes the direct and immediate cause of death. . . .

"The court reversed the order of the industrial commission and remanded the case to it with directions to allow the claimants the amount of compensation permitted by law.—Justice v. Panther Coal Co., Inc. (Va.), 2 S. E. (2d) 333."

J. C. M. C.

WECHSLER, I. S.: *Intravenous injection of paraldehyde for the control of convulsions.* J. A. M. A. **114**: 2198 (June 1) 1940.

"Sometime in 1919, during the early days of epidemic encephalitis, I had under my care one of the most violent hyperkinetic types of the disease, with extreme restlessness, toxic delirium and intractable insomnia. The course was punctuated by repeated clonic and tonic spasms of brief duration. The patient, a young man in the early twenties, was so violent in his restlessness that he had to be restrained almost all the time and required the constant attendance of two nurses by day and night. He was given all sorts of sedatives and hypnotics in large doses without effect. The barbiturates, if anything, only increased the restlessness. Paraldehyde in large doses by rectum had a transient effect, never lasting for more than fifteen minutes at a time. Spinal tap and drainage of fluid did not seem to influence the course. In sheer desperation I tried the intravenous injection of 1 cc. of paraldehyde. . . . By the time the last drop was injected, literally before the needle was withdrawn, the patient quieted down and promptly fell asleep. For the first time in two weeks he slept about two hours. The injection was then repeated, with similar results. This was followed by the administration of 1 cc. of the drug at varying intervals during the twenty-four hours, which was kept up for several days. The patient gradually improved and ultimately recovered, fortunately without any sequelae.

"Since then I have used the injection of 1 cc. of paraldehyde for convulsions of prolonged duration which did not respond to other treatment and in cases of status epilepticus. In most instances the convulsions ceased promptly; in some the effect was neither prompt nor lasting, and even a repetition of the injection failed, on rare occasions, to have the desired result. . . .

"The paraldehyde injection is so simple that it should be used in all cases of extremely prolonged or rapidly recurring convulsions. It is not indicated in the simple fit of comparatively brief duration. That generally ceases by itself and needs nothing to control it. The intravenous injection may be used with impunity in states of excitement and delirium with hyperkinesis and insomnia." Bibliography —14 references.

J. C. M. C.

ELLIOTT, JOHN, TATUM, W. L., and NESSET, N.: *The use of plasma as a substitute for whole blood.* North Carolina Med. J. 1: 283–289 (June) 1940.

"Following a study by McKenzie in 1935 of the fate of the plasma proteins in acute abdominal infections, the need was recognized for simplified equipment for the transfusion of blood that would permit its storage and reduce the reaction rate. . . .

"Blood transfusion equipment which enables a single operator without assistance to collect blood aseptically is now universally available. Blood so collected can be safely stored without special refrigeration. Reports of its use in thousands of cases indicated that it is satisfactory, and with proper attention to the preparation of donors and recipients' sets, reactions from transfusion have been materially reduced by its use. A technique for the aseptic removal of plasma from fresh or out-dated blood has been developed. . . . Incompatible plasma has been administered in a large series of cases without reaction, and the intramuscular route for its administration has been found to be possible, practical, and satisfactory when the intravenous administration is impossible or impractical. The original suggestions for the use of plasma as a substitute for whole blood have been found to be rational, and its scope of usefulness has been enlarged by many additional indications. . . .

"From our survey of the literature, we felt that successful experimental work on animals had demonstrated that serum or plasma could be used as a substitute for whole blood. For this reason we eliminated experimental work on dogs and started the use of plasma in man.

"The search for a simple aseptic technique for the collection and storage of whole blood led to the development of a technique for the preparation and preservation of plasma. Using out-dated stored blood as a source for plasma led to a study of stored blood to determine its optimum storage period. This was determined as five days. It is, of course, recognized that blood can be safely stored for a much longer period, but, from our own work and reports in the literature, we feel that the five day period is the optimum.

"A five day storage period would naturally result in the wastage of a considerable quantity of blood. Converting out-dated blood into plasma, which can be preserved for a much longer period, eliminates wastage. . . . As we have examined the indications for transfusion, we have become convinced that the plasma fraction is of even more importance than the cellular fraction.

"Indications for the use of plasma as a substitute for whole blood [are] shock, without hemorrhage . . . , shock due to hemorrhage . . . , burns . . . , infections . . . , hypoproteinemic edema . . . and convalescent plasma. . . .

"Freshly collected blood is the ideal source of plasma. If fasting donors are used, as they should be, the prepared plasma will be clear and straw colored. However, if plasma is separated from blood during the first twenty-four hours after collection, occasionally a large quantity of fibrin will settle out. We have found it advisable to store blood from twenty-four to forty-eight hours before removing the plasma.

"Out-dated bank blood is another source of plasma. If the optimum storage period is observed, plasma prepared from such blood will be almost as clear and free of hemoglobin as that prepared from fresh blood.

"An almost inexhaustible source of blood for plasma exists in the hypertensive patients who are relieved by the withdrawal of 500 or 600 cc. of

blood at intervals of from one to six months. . . .

"Early in our work it became evident to us that if plasma was to be generally available the technique for its preparation would have to be simple and aseptic. . . .

"Blood is collected and citrated in the Transfuso-Vac. After storage from one to five days it is transferred to centrifuge bottles through a simple transfer system, care being taken *not to shake the bottle of blood or stir up the red cells* which have sedimented. This is accomplished through releasing the residual vacuum in the Transfuso-Vac by inserting a sterile needle in the free hole in the rubber stopper, *not in the air tube.* The transfer system is inserted in the free hole and a needle in the air tube opening. The bottle is carefully inverted and the blood allowed to run into the centrifuge bottle. The first 250 cc. centrifuge bottle will contain approximately 90 per cent. red cells and 10 per cent. plasma. The other two bottles will contain most of the plasma and very few red cells. We do not centrifuge the first bottle, but put it in the refrigerator to be diluted with salt solution and administered as cells if we have a patient with an anemia who does not need plasma. These cells should not be used if they are older than five days. The plasma in the other two bottles is separated by centrifuging at about 2000 r.p.m. for about one hour. When the centrifuge comes to rest a swirl of cells will, at times, be noted in the supernatant plasma. It is imperative that all cells be removed from plasma that may be stored for a long period. The centrifuge bottles are placed in a refrigerator overnight, so that all of the cells will settle out. The next morning the supernatant plasma is aspirated from the centrifuge bottles to storage bottles (Plasma Vacs), which contain 250 cc. of dextrose and salt solution in a vacuum. One cubic centimeter of 1 per cent. merthiolate per 100 cc. of solution is added through the X mark in the rubber stopper as a preservative.

"The final concentration of merthiolate will be 1–10,000. This has been found to be not only bacteriostatic but also bactericidal. Cultures of 301 plasmas prepared by this technique were found sterile in every instance. Six had traveled 37,000 miles through South America at room temperature and were found sterile after six months.

"Merthiolate is an effective antiseptic in a concentration of 1–10,000 in plasma. There is no interaction between it and protein. As much as 50 cc. of 1 per cent. solution of merthiolate has been injected intravenously in a single injection into a human subject. A total quantity of 180 cc. divided into five doses has been given to one person with no demonstrable toxic effects.

"A final concentration of 2.5 per cent. dextrose in physiological salt solution was used as our first diluent. This was later changed to physiological salt and sodium citrate solution. Plasma stored in the latter diluent changed color and developed a black precipitate. These changes were not observed in plasma preserved at room temperature for 18 months in the dextrose diluent. We have concluded from these observations that dextrose in the diluent is advantageous. . . .

"Contamination by micro-organisms has not occurred in more than 500 preparations of plasma, 301 of which were cultured. Bottles of plasma preserved with merthiolate in a concentration of 1–10,000 have been exposed to the air at room temperature for periods up to six months. Frequent cultures have been found sterile.

"Following the administration of 53 preserved plasmas, stored at room temperature for periods up to nine months,

no reactions have been noted. Some of these plasmas were prepared from blood stored as whole blood for as long as eleven days, and contained considerable amounts of hemoglobin.

"Changes in color have been found to be due to the reduction of free hemoglobin, which is present in some degree in all plasma.

"Precipitates, other than fibrin, will appear in all preserved plasma after a month or so. The amount will vary, plasma prepared from non-fasting donor blood developing more precipitate than that prepared from fasting donor blood. . . .

"The use of plasma as a substitute for whole blood has two great advantages. First, it is a means of preventing the wastage of blood in institutions where blood is stored. Second, it provides a therapeutic aid to the emergency treatment of shock and hemorrhage that is not ordinarily available in all institutions. If it were necessary to type and cross match plasma immediately before its use, one of the greatest advantages which it has would be lost.

Although the use of plasma without typing or cross matching is still a debatable question, nevertheless a sufficiently large number of infusions have been given to feel that it is at least as safe as the administration of whole blood. To date, thousands of transfusions of plasma to incompatibles have been given without a single report of a reaction ascribable to incompatibility. . . .

"However, a procedure is being developed that will assure the safety of the administration of untyped plasma to incompatible recipients in every case regardless of quantity infused. The danger from the administration of incompatible plasma can only be from the use of the rare high titre plasma. To eliminate this occasional high titre plasma we are suggesting that the titre of all plasmas prepared be determined, and that those under 1 to 100 be used universally and those over that titre be segregated for use as type specific plasma. This procedure will permit the use of the majority of the plasma as universal plasma and eliminate any danger from the occasional high titre plasma.

"Group AB plasma is perfect universal donor plasma, as neither agglutinin is present. Group O recipients are universal recipients of plasma because they have no agglutinogen in their red cells.

"Group O recipients account for approximately 45 per cent. of all recipients and can receive high titre plasma. Large quantities of incompatible plasma have been given safely to single recipients.

"The same technique is followed in the administration of plasma as in the administration of whole blood. Filtration is essential, and the stainless steel filter now available is ideal for that purpose. It is unnecessary to warm plasma, as it can be administered at any temperature from refrigeration to body temperature. . . . We have given 152 incompatible plasmas and 212 plasmas without knowing the blood group of donor or recipient. No reaction resembling an incompatible blood reaction has been noted. . . .

"We have found that plasma is absorbed from the extra-vascular spaces almost as readily as physiological sodium chloride solution, and that when salt solution is not absorbed, plasma is not. Plasma is more readily absorbed from the muscle tissue than it is from subcutaneous tissue. Absorption probably occurs by way of the lymphatics, and possibly through the capillaries when the need is great. Discomfort from the intramuscular infusion of plasma seems to be no greater than that from salt solution. . . . The simplicity of the intramuscular infusion increases

the use of plasma in subjects whose veins are difficult or impossible to enter. . . .

"Reactions following plasma infusions have been negligible, only 3 occurring in our series of 445 administrations—an incidence of .68 per cent. The three occurred almost consecutively, one plasma being given without reaction between the first and second reactions. All were typical pyrogen reactions, initiated by a chill, followed by a 2 to 4 degree rise in temperature, with a return to normal in about four hours. An investigation revealed the fact that the operating room force had been so busy that recipients' sets were not cleaned and sterilized immediately after use, but were allowed to soak in salt solution at room temperature for about forty-eight hours. Previous experience had taught us that reactions could be expected under these circumstances." Bibliography—38 references.

J. C. M. C.

ROVENSTINE, E. A.: *The economics of an anesthesia service in a large municipal hospital.* Current Researches in Anesth. & Analg. **19**: 145–149 (May–June) 1940.

"The word economics is used in this discussion for convenience. . . . Economics deals with impersonal relationships which are involved in the production and distribution of wealth or relations of individuals as classes such as trade unions, and the application of these relations to problems of government. Anesthesia must deal more particularly with personal relations between the physician and his patient. . . .

"[A] recital of the activities of an anesthesia service in a large municipal hospital gives some authority to the stated belief that the most economical department of anesthesia for this or a similar institution is one composed of graduates in medicine exclusively, and that such an organization will bring most profit to the hospital, its staff and its patients. Measured in terms of finances the figures quoted add evidence to the assertion that such an organization is not a financial burden to the hospital."

J. C. M. C.

AMBLER, A. C.: *The present status of anesthesia.* North Carolina Med. J. **1**: 244–249 (May) 1940.

"The advent of new drugs and new equipment and the development of new techniques, within the past few years, have increased research and study of anesthesia. . . . Anesthesia has developed today into a highly specialized field engaged in by physicians who have been trained as experts and who by their training are qualified to choose and administer a particular type of anesthesia to each individual case. . . .

"Inhalation anesthesia continues to be most universally used. Spinal anesthesia is becoming more and more popular, owing no doubt to a better understanding of it. Intravenous anesthesia has become remarkably popular in some localities and has not taken at all in others. The use of regional anesthesia, with the exception of spinal, has neither increased nor decreased for several years. The closed method of inhalation anesthesia—that is, rebreathing with the carbon dioxide absorption technique—is now universally used. However, the open method remains the safest for the occasional anesthetist and for the person who has not been trained. . . .

"Dr. Ralph Waters at the University of Wisconsin recently stated that we will not have an ideal anesthesia as long as the patient is not breathing atmosphere to which he is accustomed. Nevertheless, closed ether is much more satisfactory to patient, surgeon, and anesthetist than open ether, even

though there is normal atmosphere with open ether. We are trying at present the use of compressed air as a diluent and carrier. I have also used the inert gas helium, only to find that it is easier to allow the patient to inspire normal air occasionally and to expire into the breathing bag. This will keep some air with its nitrogen and other inert gases in the mixture. It may be coincidence, but our atelectatic cases have been rare. It is reasonable to assume that with our rapidly absorbable anesthetic mixtures, together with the disappearance of nitrogen from the mixture (which eventually occurs in a closed circuit), we are inviting atelectasis by the absence of any sustaining inert gas.

"It is highly important that a free airway be established at all times, not only for good anesthesia but for the prevention of atelectasis and the building up of a high carbon dioxide content. . . . Intra-tracheal catheters of course offer the best artificial airways. . . .

"The anesthetist's first duty is to the patient, and he must exercise every precaution, anticipate every untoward change and be prepared to cope with any situation. . . .

"With the increased use of explosive anesthetic agents there have naturally been several explosions with their resultant publicity. The American Society of Anesthetists, Inc., began an intensive investigation about two years ago, and I believe their committee is still functioning. They investigated every explosion or fire for the past twenty years about which they could obtain any information. The committee has reported that a large percentage of the explosions were preventable. . . .

"Divinyl ether (marketed commercially as Vinethene) is a new inhalation agent which has stood a thorough clinical investigation and is now accepted. . . . Ethyl chloride as a general agent, in my opinion, has but two uses or indications. First, in doing a paracentesis of an eardrum on a child in the home; and, second, in the extraction of deciduous teeth. It must only be used for induction. . . . Chloroform is still used in England and in Europe, but in this country its use is limited. . . . Ether remains our safest and most popular inhalation agent. . . . Nitrous oxide still commands a definite place among anesthetic agents. It is nonexplosive and is therefore indicated when the cautery or electro-surgical units are to be used about the head or neck, or for cauterizing the lung in lung abscess. It is valuable as an inducting agent for ether and ideal as an analgesia in the first stage of labor. With the exception of these indications, the writer has not used nitrous oxide in several years. . . . Ethylene is explosive. It allows a greater percentage of oxygen than nitrous oxide, and gives a little more relaxation. Ethylene has been supplanted entirely by cyclopropane. Cyclopropane has been in general use about seven years. During this time it has earned for itself the top rank in gaseous agents. . . .

"The practice of 'blowing out' a patient by the use of CO_2 after an anesthetic is not recommended, because of the possibility of inspiring foreign material, saliva, or mucus, and the chances of promoting acidosis. Helium is being used to a small extent as a part carrier in obstruction cases and as an inert gas.

"Intravenous anesthesia is becoming more popular each year. It has many advantages during certain procedures and there are many distinct indications for its use. Pentothal-sodium seems to be gaining more friends than evipal. It is our experience that pentothal acts more smoothly and that the patients seem to behave better. We use intravenous drugs only when specifically indicated, and not routinely.

"Avertin by rectum has largely supplanted ether and paraldehyde by rectum. Although avertin occasionally produces surgical anesthesia, it should never be given for this purpose, but only as a basal anesthetic. . . .

"As stated previously, spinal anesthesia is becoming more popular—probably because we have a better understanding of its use and are not getting the bad results we did a few years ago. There are still some surgeons and anesthetists who do not avail themselves of the advantages that spinal anesthesia offers, while others use it too recklessly, without proper understanding of its dangers and limitations. When spinal anesthesia was first introduced its use was advocated in the bad heart cases and in poor risks. Now we know that the patient must be in good general condition. The cases must be selected. . . .

"Concerning blocks, I will only mention that caudal and transsacral blocks are now being replaced by low spinals. Novocain in the fifth lumbar space is easier to give, requires less time, gives better anesthesia, and has less general effect on the patient."

J. C. M. C.

NEFF, WILLIAM: *The continuous recording of systolic blood pressure during anesthesia.* Current Researches in Anesth. & Analg. **19**: 175–179 (May–June) 1940.

"A method for the continuous graphic recording of pulse and respiration during anesthesia has previously been presented. . . . The desirability of obtaining a continuous blood pressure record simultaneously was emphasized at that time. Subsequently, the practicability of incorporating into our unit the combined optical and electrical mechanism described by Doupe, Newman and Wilkins . . . was discussed with one of them (Newman). Accordingly, a unit so modified as to render its use in the operating theater practical was built into our recording anesthetic machine. . . .

"The method employed is essentially a double cuff system consisting of . . . :

"1. An inflated upper cuff containing a constant leak. A side-arm from this cuff is attached to a pressure manometer. 2. A snug lower cuff which transmits the pulsation beneath to a diaphragm upon which is fixed a mirror. 3. A combined optical and electrical mechanism which activates an electromagnetic intake valve resulting in the inflation of the upper cuff. Adjustment of the amount of the leak and the pressure permitted to enter the upper cuff during each opening of the intake valve results in the cuff being automatically maintained at the systolic blood pressure level. . . .

"It is not to be claimed that a continuous blood pressure record during the course of every anesthetic is necessary. . . .

"Clinical studies of the respiratory and circulatory effects of vasopressor and vasodilator drugs can be made with the apparatus, and its sphere of usefulness is by no means limited to anesthesia."

J. C. M. C.

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EDITORIAL POLICY

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